University of Nottingham
UK | CHINA | MALAYSIA

Risk stratification of chronic liver disease in the community

Dr Rebecca Harris

Thesis submitted to the University of Nottingham for the degree of Doctor of Philosophy

September 2018

Table of Contents

Abstract i

Published papers from this thesis v

Acknowledgements vi

Abbreviations viii

1 Introduction 1

1.1 Natural history of chronic liver disease 1

1.2 Cirrhosis incidence, prevalence and mortality 4

1.2.1 Alcohol related liver disease 7

1.2.2 Non-alcoholic fatty liver disease 10

1.3 Limitations of current diagnostic tests 14

1.3.1 Liver function tests 15

1.3.2 Ultrasound 17

1.3.3 Liver biopsy 18

1.4 The rationale for changing current clinical practice 20

1.4.1 Chronic liver disease as a public health priority 20

1.4.2 An opportunity to implement new diagnostic pathways 21

1.5 New non-invasive diagnostic tests for liver fibrosis 22

1.5.1 Transient elastography 23

1.5.2 Enhanced Liver Fibrosis (ELF) score 25

1.5.3 Summary of other non-invasive tests 26

1.6 Aims 32

2 A systematic review of the use of non-invasive tests in a community setting to stratify for alcoholic and non-alcoholic fatty liver disease 34

2.1 Chapter summary 34

2.2 Introduction 34

2.3 Aims 36

2.4 Methods 37

2.4.1 Search strategy 37

2.4.2 Selection criteria 38

2.4.3 Data collection 39

2.4.4 Outcome measure 40
2.4.5 Meta-analysis 40
2.5 Results 42
2.5.1 Non-invasive tests used 42
2.5.2 Target population 42
2.5.3 Screening uptake 43
2.5.4 Prevalence of fibrosis 44
2.5.5 Prevalence of cirrhosis 46
2.5.6 Liver biopsy results 46
2.5.7 ALT levels and predictors of significant liver disease 47
2.5.8 Predictors of clinically significant liver disease 48
2.6 Discussion 62
3 Obesity as a risk factor for chronic liver disease. How important is it? Risk stratification using transient elastography in a community setting 69
3.1 Chapter summary 69
3.2 Introduction 70
3.2.1 Transient elastography as a risk stratification tool 70
3.2.2 Previous work by our research group 71
3.2.3 Obesity as a risk factor for chronic liver disease 72
3.2.4 Aims 73
3.3 Methods 74
3.3.1 Study approvals 74
3.3.2 Study setting 74
3.3.3 Patient selection 75
3.3.4 Transient elastography 76
3.3.5 Enhanced liver fibrosis (ELF) scores 77
3.3.6 Risk stratification pathway 78
3.3.7 Statistical methods 78
3.4 Results 80
3.4.1 Baseline characteristics of the cohort 80
3.4.2 Risk stratification of all patients 80
3.4.3 Evaluating BMI as risk factor using a different non-invasive test 92
3.4.4 Concordance between Transient elastography and the ELF score 95

3.4.5 Is the transient elastography reading being falsely elevated by a raised BMI? 95
3.5 Discussion 98
3.5.1 Principal Key findings 98
3.5.2 Strengths and weaknesses 99
3.5.3 Relevance to clinical practice 102
3.6 Conclusion 105
4 The XL probe: a luxury or a necessity? Risk stratification in an obese community cohort using transient elastography 107
4.1 Chapter summary 107
4.2 Introduction 108
4.2.1 Transient elastography as a risk stratification tool 108
4.2.2 Limitations of transient elastography in an obese population 108
4.2.3 The XL probe 109
4.2.4 Aims 110
4.3 Methods 111
4.3.1 Study approvals 111
4.3.2 Study setting and patient selection 111
4.3.3 Transient elastography 111
4.3.4 Risk stratification pathway 112
4.3.5 Statistical methods 113
4.4 Results 114
4.4.1 Patient characteristics 114
4.4.2 Reliability of the M and XL probes 114
4.4.3 Use of the M and XL probes within the community risk stratification pathway 120
4.5 Discussion 123
4.5.1 Key findings 123
4.5.2 Strengths and limitations 124
4.5.3 Relevance to clinical practice 126
4.5.4 Conclusion 128
5 Economic evaluation of a community based diagnostic pathway to stratify adults for chronic liver disease 129
5.1 Chapter summary 129
5.2 Introduction 129

5.2.1 Chronic liver disease as a public health priority 129
5.2.2 Rationale for determining cost-effectiveness of a risk stratification pathway compared with standard care 130
5.2.3 Aims 131
5.3 Methods 132
5.3.1 Modelling approach 132
5.3.2 Diagnosis of liver disease included within the model 132
5.3.3 The risk stratification and standard care pathways 133
5.3.4 The study population 134
5.3.5 The decision-analytic model 135
5.3.6 Data sources for transition probabilities, health status and resource use 137
5.3.7 Transition probabilities 139
5.3.8 Utilities 140
5.3.9 Costs and resource use 140
5.3.10 Cost-effectiveness analysis 141
5.4 Model inputs 144
5.4.1 Transition probabilities in NAFLD economic model 144
5.4.2 Transition probabilities in the ALD model 155
5.4.3 Incorporating the effect of the risk stratification pathway (NAFLD and ALD) into transition probabilities 168
5.4.4 Utilities 171
5.4.5 Resource use and costs for both NAFLD and ALD models 173
5.5 Results: Cost effectiveness of the risk stratification pathway versus standard care in NAFLD 175
5.5.1 Base-case analysis 175
5.5.2 One-way sensitivity analyses 177
5.5.3 Multiway sensitivity analyses 178
5.6 Results: Cost effectiveness of the risk stratification pathway versus standard care in ALD 180
5.6.1 Base case analysis 180
5.6.2 One way sensitivity analyses 182
5.6.3 Multiway sensitivity analyses 183
5.7 Discussion 186
5.7.1 Key findings 186
5.7.2 Strengths of analysis 186

5.7.3 Limitations of analysis 188
5.7.4 Clinical implications 193
5.7.5 Future perspectives 195
5.7.6 Conclusions 196
6 Discussion 197
6.1 Principal findings 197
6.2 Clinical implications 198
6.2.1 Is there a need to alter our current diagnostic pathways for chronic liver disease? 198
6.2.2 Who should be targeted? 200
6.2.3 Which tool should be used to stratify? 203
6.2.4 Would changing our approach be cost effective? 205
6.3 Future work 207
6.4 Conclusion 209
7 Appendix 210
7.1 Search algorithms used within the electronic databases 210
7.2 Original risk stratification pathway used in the feasibility study by Harman *et al* [157] 213
7.3 Examples of Read codes to identify patients with a lifestyle related risk factor ... 214
7.4 Risk Stratification pathway used within the study in Chapter 3 216
7.5 An outline of the standard care pathway 217
7.6 Responses obtained from the expert panel 218
7.7 Resource use and costs 222
7.8 Assumptions and results of one-way sensitivity analyses (NAFLD model) 246
7.9 Assumptions and results of one-way sensitivity analyses (ALD model) 249
8 References 253

Abstract

Introduction

There is an appreciable undiagnosed burden of Chronic liver disease within our society with mortality rates increasing over recent decades. The reasons for this include the rise in lifestyle related risk factors (e.g. hazardous alcohol use, type 2 diabetes and obesity), the asymptomatic nature of the disease which ensures patients do not present to a clinician at an early stage, and the ineffectiveness of current diagnostic tests available to primary care physicians.

By transforming the diagnostic pathways we may be able to start proactively identifying and risk stratifying patients with liver disease. Implementation of a risk stratification pathway into a primary healthcare setting would allow a large number of patients to be stratified and identify those who would benefit from a referral to specialist services or further follow up in secondary care. The studies within this thesis have aimed to focus on determining the optimal approach to achieve this and whether this may be cost effective.

Methods

The first part of the thesis was to understand and document the current evidence on liver disease diagnosed by a non-invasive test in a community setting focusing on those patients at risk of non-alcoholic fatty liver disease and alcoholic liver disease. In addition to the prevalence of disease within the studied populations the aim was to identify which non-invasive tests for liver fibrosis have been used to stratify patients at risk and to evaluate the

difference between unselected and targeted populations. A systematic review of the literature was performed to address these aims.

The second part of the thesis was to improve our understanding of which risk factors were associated with significant liver disease. A prospective diagnostic study using transient elastography was performed to investigate this. The focus was on a raised body mass index but the interaction with alcohol and type 2 diabetes was also investigated along with the performance of the portable transient elastography device within an overweight subgroup of the study cohort.

The third part of the thesis was to gain an understanding of the cost effectiveness of implementing a new pathway for liver disease in a community setting. A health economic evaluation of this alternative approach compared with current standard care from an NHS England perspective was completed using Markov modelling to estimate long-term health and economic effects.

Results

From the systematic review, transient elastography and Fibrotest, were identified to be the most frequently used tests for liver fibrosis within a community setting and had their results compared against histological findings. Subsequently these were the most validated non-invasive tests in a general population setting. The prevalence of advanced liver fibrosis and cirrhosis in the general population was identified to be between 0.9%-2% and 0.1%-1.7% respectively with studies which targeted patients with risk factors for liver disease (e.g.

hazardous alcohol use or type 2 diabetes) reporting a higher prevalence of disease (advanced liver fibrosis (0%-27.9%), cirrhosis (2.4%-4%)).

In our prospective study, implementation of a risk stratification pathway based on the risk factors of hazardous alcohol use and/or type 2 diabetes and/or a raised body mass index saw 703 patients attend of which 82 (11.7%) had an elevated transient elastography reading consistent with clinically significant liver disease. Seventy seven percent of the cohort had a single risk factor, whilst 21.3% had a combination of two and 1.4% had all three risk factors. An elevated transient elastography reading was approximately as common in patients with just a raised body mass index (≥27.5kg/m^2) (8%) as it was in patients with more recognised solitary risk factors (Type 2 diabetes, 10%; Hazardous alcohol use 3.5%). A raised body mass index in combination with other risk factors further increased the proportion of patients with an elevated transient elastography reading and therefore demonstrated that a raised body mass index as a single or combined risk factor for chronic liver disease is important. Of the patients who attended the pathway 477 had a body mass index ≥ 28kg/m^2 and had a transient elastography reading with both the M and XL probes. Twenty one percent of these patients had no valid measurements with the M probe. The XL probe significantly increased the number of valid (M vs XL probe: 66.2% vs 90.2%, $p<0.001$) and reliable (M vs XL probe: 77.4% vs 98.5%, $p=0.028$) readings that were obtained and re-stratified 5.2% of patients to have a normal transient elastography reading. The XL probe is therefore not an optional extra but a necessity if transient elastography is to be utilised within a community setting where a raised body mass index is becoming common.

Lastly, results from an economic evaluation suggested that the risk stratification pathway was more cost effective than standard care with a cost of £2,138 per extra quality-adjusted

life-year (QALY) for patients diagnosed with non-alcoholic fatty liver disease and £6,537 per QALY for patients diagnosed with alcoholic liver disease. The models of the risk stratification pathway demonstrated ≥85% probability of cost-effectiveness at the UK willingness-to-pay threshold of £20,000/QALY.

Conclusion

The feasibility of implementing a community based risk stratification pathway for chronic liver disease is clearly shown in the systematic review. Furthermore, the burden of undiagnosed liver disease revealed in the systematic review and the prospective study challenges our current clinical pathways for liver disease. Obesity is a risk factor, in isolation and in combination with alcohol and type 2 diabetes and therefore needs to be considered in any targeted case finding strategy that is proposed. The economic evidence demonstrates that a risk factor approach is likely to be cost effective which is highly relevant in the current financial climate. This research has direct implications on the implementation of care pathways for liver disease but further research is required to refine the strategy and enable adoption into clinical practice.

Published papers from this thesis

1. **Harris R**, Harman DJ, Card TR, Aithal GP, Guha IN. Prevalence of clinically significant liver disease within the general population, as defined by non-invasive markers of liver fibrosis: a systematic review. Lancet Gastroenterology Hepatology 2017 Apr;2(4):288-297. doi: 10.1016/S2468-1253(16)30205-9.

2. Tanajewski L, **Harris R**, Harman DJ, Aithal GP, Card TR, Gkountouras G, Berdunov V, Guha IN, Elliott RA. Economic evaluation of a community-based diagnostic pathway to stratify adults for non-alcoholic fatty liver disease: a Markov model informed by a feasibility study. BMJ Open. 2017 Jul 5;7(6):e015659. doi: 10.1136/bmjopen-2016-015659.

3. **Harris R**, Card TR, Delahooke T, Aithal GP, Guha IN. The XL probe: A luxury or a necessity? Risk stratification in an obese community cohort using transient elastography. United European Gastroenterology Journal. 2018 April. doi.org/10.1177/2050640618772944

Acknowledgements

Firstly I would like to thank my three PhD supervisors Dr Neil Guha, Dr Tim Card and Professor Guru Aithal. I am grateful for your continued support, insight and constructive feedback on my academic work. I have learnt a lot about myself during this journey and thank you for your guidance.

A thank you to the Academic Health Science Network (AHSN) who have funded my post and in particular to Mr Nick Hamilton who has made working on the Scarred Liver Project all the more enjoyable.

Thank you to the whole team at the Nottingham Digestive Diseases Biomedical Research Centre who have supported my work and on many occasions have been a useful listening ear when unexpected challenges occurred.

To my specialist Fibroscan nursing duo, Mary and Angela. A continued enthusiasm for any work thrown your way has made implementing the Scarred Liver Project much easier and you have been a large part of its ultimate success.

The liver lobule – now made up of many members – have been a joy to work with and made coming into work a pleasure not a chore. There have been many laughs had in the office and I leave it with a tinge of sadness but thankful that I have made some true friends along the way.

To my parents, who despite my continued self-doubt have always believed in and supported my dreams. Thank you for your continued encouragement.

To Alec, my pillar of strength and partner in life. Thank you for your continued love and support. I could not be where I am without you and am grateful that I have you by my side to tackle life together.

And lastly to Jack, who came tumbling into our lives during the middle of this adventure. Every day you bring us joy and have helped to give me a different perspective on the challenges that occur. I hope that one day you will also have the courage to strive for and achieve your dreams. To my beautiful baby boy, this thesis is dedicated to you.

Abbreviations

ALD= Alcoholic liver disease

ALT = alanine aminotransferase

AST = aspartame aminotransferase

APRI = AST:platelet count ratio

AUDIT = Alcohol use disorders identification test

BAAT = score of age≥50 years (1 point), body mass index≥28 kg/m^2 (1 point), ALT≥2 times upper limit of normal, triglycerides≥1.7mmol/L

BARD = weighted score of Body mass index ≥28kg/m^2 (1 point), AST:ALT ratio≥0.8 (2 points), Type 2 Diabetes (1 point)

BMI = body mass index

CC = Compensated cirrhosis

CLD = Chronic liver disease

DC = Decompensated cirrhosis

Dx = Diagnosis

EASL = European association for the study of liver

ELF = Enhanced Liver Fibrosis (combination of hyaluronic acid, TIMP metallopeptidase inhibitor 1 and Procollagen III N-Terminal Propeptide)

FIB4 = combination of age, ALT, AST and platelet count

HCC = Hepatocellular carcinoma

HCV= Hepatitis C virus

ICER = Incremental cost effectiveness ratio

kPa = kilopascals

LFT(s) = Liver function test(s)

LSM = liver stiffness measurement

MeSH = Medical subject headings

NAFLD = Non-alcoholic fatty liver disease

NASH = Non-alcoholic steatohepatitis

NFS = NAFLD Fibrosis Score (combination of age, hyperglycaemia, body mass index, platelet count, albumin, and AST:ALT ratio)

NHS = National Health Service

NICE = National Institute for Health and Care Excellence

NMD = no/mild disease

OR = Odds Ratio

QALYs = Quality adjusted life years

QoL = Quality of life

RCT = Randomised control trial

SC = Standard care

SCD = Skin capsular distance

SLD = significant liver disease

T2DM = type 2 diabetes

TE = Transient Elastography

UK= United Kingdom

WHO = World Health Organisation

1 Introduction

1.1 Natural history of chronic liver disease

Chronic liver disease has a protracted natural history and encompasses a spectrum of histopathological features ranging from simple steatosis, through to steatohepatitis, fibrosis and ultimately cirrhosis.

It has been demonstrated that a persistent insult to the liver causes a cycle of inflammation, chronic damage and an accumulation of extracellular matrix proteins which distorts the hepatic architecture by forming fibrosis[1]. Subsequently, nodules develop from the regenerating hepatocytes and histologically this represents cirrhosis, the end stage of chronic liver disease irrespective of the underling aetiology. Several semi quantitative grading systems have been created to describe and evaluate this process reflecting the location and extent of fibrosis within the liver [2-4]. Different histological scoring systems exist depending on the underlying aetiology but roughly these equate to the following: no fibrosis (stage 0), perisinusoidal fibrosis (stage 1), portal fibrosis (stage 2), bridging fibrosis (stage 3) and cirrhosis (stage 4). This process develops over many years following a continued insult to the liver which could be as consequence of continued alcohol misuse, a chronic infection such as Hepatitis C or an excessive build-up of fatty deposits secondary to insulin resistance in some metabolic diseases.

A crucial and unique quality of the liver is that it can regenerate; leading to a regression of disease if the insult is removed or lifestyle modifications are undertaken[5]. Historically, liver fibrosis was thought to be irreversible however recent advances in the understanding of the

complex cellular and molecular pathways underlying this process have demonstrated new therapeutic targets which could be utilised to develop future treatments and may allow the reversal of fibrosis[6]. To date, no anti-fibrotic treatments have been implemented into clinical practice but development continues in phase II/III clinical trials.

Although cirrhosis is the histological end point of this process there remains a phase within the natural history when the patient can still be asymptomatic, this is termed compensated cirrhosis. During this phase hepatocyte dysfunction can start to occur coupled with increasing intrahepatic resistance to blood flow. This may result in hepatic insufficiency and portal hypertension causing the patient to enter a rapidly progressive phase termed decompensated cirrhosis. Portal hypertension develops once the pressure gradient crosses the threshold of 6mmHg although complications do not start to occur until portal pressure crosses a critical threshold of 10mmHg; at this point it is termed clinically significant portal hypertension[7, 8]. Variceal bleeding and ascites are more likely to occur once the portal pressure rises above 12mmHg. Thus treatments have been aimed to prevent the portal pressure rising above this threshold which could consequently reduce the likelihood of a decompensation event occurring and ultimately improve long term survival [9, 10].

The development of any complication of cirrhosis which includes ascites, encephalopathy, variceal bleeding or jaundice clinically represents the time point at which a patient transitions from compensated to decompensated cirrhosis. This has been further categorised into four different clinical stages following a review of two large natural history studies which included 1649 patients[11]. The four stages are defined by the presence or absence of specific complications and were agreed at the Baveno IV conference in 2005[12]. Stage 1 is defined by the absence of either varices or ascites while in stage 2 varices must be

present; collectively these two stages correspond to patients with compensated cirrhosis. Data from a recent cohort study which included 4537 patients with liver cirrhosis identified from the UK General Practice Research Database (GPRD) was analysed to determine the rate of decompensation once a patient was diagnosed. Patients who were categorised as stage 1 or 2 had an absolute risk of death in the first year following diagnosis of 7.2% and 6.6% respectively[13]. Stage 3 of the Baveno IV classification is defined by the presence of ascites with or without varices. Whilst in stage 4 a variceal bleed must have occurred although ascites does not necessarily have to be present. The latter two stages correspond to decompensated cirrhosis where the absolute risk of death in the first year following diagnosis has been reported as 20.1% and 18.2% for stages 3 and 4 respectively[13].

The same cohort of patients identified from the UK GPRD were also matched to a control cohort and those with compensated cirrhosis were demonstrated to have nearly a five-fold increased risk of death (HR 4.7, 95% CI 4.4– 5.0) compared to the general population[14]. For those with decompensated cirrhosis the risk was nearer 10 fold (HR 9.7 95% CI 8.9-10.6)[14]. In the same study the 1 and 5 year survival rate for patients with compensated disease was 87.3% and 66.5%, respectively, compared to 75.0% and 45.4% for patients who have decompensated disease[14]. Ratib *et al* also demonstrated that hospitalisation of a patient with liver cirrhosis marks a downturn in survival and mortality is significantly increased compared to a similar group of patients who remain ambulatory (HR = 2.78, 95% CI 2.53, 3.06); this was shown to be independent of the Baveno IV classification[15].

Given the clear difference between the mortality rates of those patients who are compensated compared to those who have decompensated it is imperative that measures are undertaken to diagnose patients prior to these events occurring and subsequently

employ interventions to stop patients' disease progressing which may necessitate an admission to hospital. However, it has been demonstrated that patients are currently being diagnosed late within their natural history when features of decompensation are already present. Ratib *et al* identified 5118 incident cases of liver cirrhosis between January 1998 and December 2009 using the Clinical Practice Research Datalink (CPRD) and linked English Hospital Episode Statistics and reported that 47.3% of patients only received their diagnosis of liver cirrhosis following an emergency admission to hospital[15]. Of the incident cases identified, 43.7% were decompensated (Baveno IV stages 3 or 4) at the time of diagnosis[16]. This is a reflection of the large burden of undiagnosed chronic liver disease in the community and that current referral pathways and diagnostic tests used to identify these patients are ineffective.

1.2 Cirrhosis incidence, prevalence and mortality

Chronic liver disease is an increasing health burden worldwide and consequently has a large impact on global morbidity and mortality. The Global Burden of Disease study in 2010[17, 18] reported that 2.0% of all deaths were attributable to liver cirrhosis while another 1.4% were attributable to liver cancer. It also reported disability adjusted life years (DALYS) as a measure of morbidity demonstrating that 2.0% of all DALYs were secondary to liver cirrhosis or cancer. There are significant variations in mortality among different regions of the world with Mokdad *et al[19]* reporting liver cirrhosis as a health priority in Central Asia, Central Europe, Eastern Europe and Central Latin America.

The World Health Organisation reports that 1.8% of all deaths in Europe can be attributed to liver cirrhosis with the highest rates in south-eastern and north-eastern areas[20]. While most of Europe has seen a decline in their mortality rates secondary to cirrhosis, rates within

England and Wales continue to rise[20]. A 69% increase was observed between the periods of 1987-1991 and 1997-2001; the steepest in western Europe[21].

In the UK, the standardised mortality rates for liver disease since 1970 have increased by 400% [22], which has been shown to be the exception compared to all other common causes of death such as cardiovascular disease in which the standardised mortality rate over the same time period has more than halved. In 2011, The Office of National Statistics in the UK identified liver disease as the third largest cause of premature death with 62,000 years of working life lost each year[22, 23]; only ischaemic heart disease and self-harm were greater causes of premature death. More than one in ten deaths from liver disease occur in people in their 40s and overall 90% of deaths will occur in people under the age of 70[24]. The average age of death is currently only 59 years of age[25]. Inequalities across England also exist with mortality rates in the north higher than the south[26]. This is thought to be a reflection of the different prevalence of risk factors within these areas[27] but data within the recently published Atlas of variation in risk factors and healthcare for liver disease in England has also highlighted the geographical variation in healthcare provision which may be contributing to these outcomes[26].

The majority of chronic liver disease in the UK results from lifestyle related risk factors including alcohol misuse, obesity and type 2 diabetes which are all preventable if specific interventions are employed however the prevalence of these risk factors continues to rise within the general population[20, 21, 27]. This therefore explains why alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) are now the most common causes of chronic liver disease in the UK and the Western world[20, 27]. The incidence of cirrhosis in the UK was reported by Fleming *et al* [28] who reviewed the UK GPRD between 1992 and

2001 and identified 3360 incident cases of cirrhosis. The crude incidence at this time was 14.44 per 100,000 person years with a 45% increase during the time period that was studied. The incidence of cirrhosis was reported to be higher in men than women (incidence rate ratio 1.52; 95% CI 1.42-1.63) and a statistically significant increase in both alcoholic cirrhosis and non-alcohol related cirrhosis was seen across the 10 year period. The study also provided the most up to date estimates of cirrhosis prevalence and in 2001 this was reported to be 0.076% with a reported 68% increase across the time period studied[28]. The same research group recently updated these estimates using UK CPRD and linked English Hospital Episode Statistics to identify 5118 incident cases of cirrhosis between 1998 and 2009. During this 12 year period the crude incidence rate had increased by 50.6% with increases seen for both men and women and in all aetiology types[16].

A complete understanding of the epidemiology of chronic liver disease is limited by a lack of a national registry and the usual prerequisite for a decompensating event to have occurred before chronic liver disease is documented on a death certificate. A stigma also continues to be attached to the underlying risk factors e.g. alcohol, hepatitis C, and consequently the true incidence and prevalence within these disease groups remains unknown. The nomenclature can also cause confusion with the use of non-alcoholic fatty liver disease (NALFD) used to describe not only patients with hepatic steatosis but also those with significant liver fibrosis and cirrhosis.

1.2.1 Alcohol related liver disease

1.2.1.1 Prevalence and mortality

Alcoholic liver disease defines a spectrum of disease ranging from simple steatosis, steatohepatitis, fibrosis and cirrhosis. Simple steatosis has been reported to develop in 90% of people who drink more than 60g of alcohol per day[29]. This is often self-limiting and can be reversed if abstinence is achieved.

The incidence and prevalence of alcohol related liver disease among the general population or even in those who are hazardous alcohol drinkers is not well known. In the study by Fleming *et al* which reported the incidence of cirrhosis in the UK, 38% of the study population had a record of alcohol as their underling aetiology[28]. In the subsequent study by Ratib *et al* this proportion had increased to 53.9% with a higher proportion of men than women defined as having alcoholic cirrhosis (61.9% vs 42.8%, respectively)[16].

Excessive alcohol consumption has long been acknowledged as the predominant risk factor for chronic liver disease. In 2010, alcohol consumption was responsible for 3.8% of all-cause mortality worldwide whilst alcoholic liver cirrhosis specifically was responsible for 0.9% of all-cause mortality and over 14 million disability adjusted life years (DALYs) [30, 31].

In Europe, between 1959 and 2002, a divide between the east and west has been observed with increased mortality rates in the south eastern and north eastern countries including Finland and the United Kingdom whilst countries in central Europe such as Germany and France have demonstrated declines in their mortality rates. It has been hypothesised that

this pattern reflects the consumption of alcohol within those countries[32] and is supported by the fact that France implemented public health policies to control the consumption of alcohol whilst in England advertisements on alcohol are not as restrictive and cheap alcohol is still easily accessible. In the UK, deaths from known causes of liver disease increased fourfold between 1980 and 2013 with 84% of the increase secondary to alcohol related disease[33]. This correlates closely with the consumption of alcohol on a population level and in the UK alone the alcohol consumption of the population doubled between 1960 and 2002.

1.2.1.2 Hazardous alcohol use

Hazardous alcohol use is one of the most significant and avoidable lifestyle related risk factors which has an effect on over two hundred acute and chronic conditions including pharyngeal and oesophageal cancer, stroke and hypertension. However most deaths continue to be liver related [34] The price of alcohol has decreased substantially so that consequently drinks are now 54% more affordable than in 1980[35]. Unsurprisingly this correlates with an increase in associated harms and healthcare use and between 2010 and 2016 alcohol related admissions increased by approximately 17% [36].

In the UK, approximately a quarter of adult patients who present to primary care are hazardous alcohol drinkers and drink above the previous recommended weekly limits of 21 units for men and 14 units for women [22, 37]. The upper limit of safe drinking set by the Chief Medical Officer has recently been reduced further to 14 units per week for both men and women who drink regularly to reflect the harms that hazardous alcohol use can cause[38]. However, ten million adults still regularly drink more than 14 units of alcohol each week [26] and furthermore 10% of the population would be classified as harmful drinkers by exhibiting signs of psychological or physical harm as result of their alcohol intake. Alcohol

misuse also extends to those under 18 years of age with 65% of 15 and 16 years old reported to have drunk alcohol in the previous month and an estimated 11 million units of alcohol consumed each week by those aged 11-17 years old[39, 40].

Alcohol abstinence represents the Holy Grail which if undertaken successfully can allow the liver to regenerate and lead to improved clinical outcomes and regression of disease [31, 41]. However, a rise in alcohol related liver disease continues to occur despite the implementation of brief intervention within clinical studies reporting positive results. Kaner *et al* completed a meta-analysis of 21 randomised control studies which demonstrated that brief intervention in primary care is effective and in comparison to a control group can reduce average alcohol consumption by 41 grams per week (95% CI, -57 to -25) [42]. A recent update of this analysis included 69 studies and a total of 33,642 participants who were randomised to receive brief intervention to reduced harmful or hazardous alcohol use. This meta-analysis confirmed the previous results, however it also reported that a longer duration of counselling probably had little additional effect[43]. This was reflected in a previous cluster randomised control trial which did not demonstrate a statistically significant difference in the reduction of hazardous or harmful drinking between three different methods of brief intervention which included brief advice, brief lifestyle counselling and the provision of a patient information leaflet[37]. However, a body of evidence in the literature does support the use of these strategies compared to no intervention at all and yet they are reported to be implemented poorly within clinical practice[42, 44].

1.2.1.3 Societal impact

Alcohol related harm is reported to cost the NHS £3.5 billion[36, 39] per year and the economy £7.3 billion due to unemployment, absence from work due to ill health, early retirement and premature deaths among economically active people of working age[36].

Working years lost due to alcohol rose from 46,000 in 2010 to 167,000 in 2015; 16% of the total number in England. Alcohol misuse also has an impact on the wider society including child services, road traffic accidents and alcohol related crime. Overall alcohol misuse has been estimated to have a total societal cost in England and Wales of £21 billion per year with estimates reportedly as high as £52 billion.

1.2.2 Non-alcoholic fatty liver disease

1.2.2.1 Incidence, prevalence and mortality

Non-alcoholic fatty liver disease is diagnosed when hepatic steatosis is evident in the liver, either on histology or imaging, and no secondary cause can be identified such as significant alcohol consumption, concomitant medications or a hereditary disorder. The presence of only steatosis in the liver is categorised as non-alcoholic fatty liver (NAFL) while the additional features of ballooning and intra-acinar and portal inflammation is defined as non-alcoholic steatohepatitis (NASH)[3]. NASH can be present with or without fibrosis being evident and was first described by Ludwig *et al* in 1980[45]. Persistent inflammation can lead to the development of fibrosis and ultimately cirrhosis.

The incidence of NAFLD in the general population has been difficult to ascertain and has resulted in a wide range of estimates worldwide. Whalley *et al* reported an incidence of 29 cases per 100,000 person years following analysis of the International Classification of Diseases, Tenth Revision (ICD-10) codes from a new outpatient Hepatology clinic[46]. However, given the inaccuracy of administrative coding and that this represents a pre-selected cohort which will have its own inherent referral bias the true incidence has subsequently been demonstrated to be much higher. Using ultrasonography, incidence rates

have been reported to be 29.7 per 1000 person years[47] and using proton-magnetic resonance spectroscopy to measure intrahepatic triglyceride content (IHTG) the population incidence of NAFLD was reported to be 34 per 1000 person years[48].

Non-alcoholic fatty liver disease is highly prevalent within the general population although this estimate varies depending on the population being studied and the diagnostic tool being used. Screening studies which have used ultrasonography have reported a prevalence of between 20-30%[49, 50] while use of elevated liver transaminases as a non-invasive marker of NAFLD have reported a prevalence of 8% to 9%[51, 52]. In studies using a liver biopsy and thus a proven histological diagnosis an even wider prevalence of disease has been reported. A Korean cohort being investigated as potential liver transplant donors reported NAFLD in 51%[53] while a similar cohort in the United States identified 20% of the donors to be ineligible due to a high degree of steatosis[54]. However, Younossi *et al* [55]has recently reported the results from a meta-analysis of 86 studies which included a sample size of more than 8 million patients to estimate the global prevalence of NAFLD. A worldwide prevalence of 25.24% was reported with the highest estimates in the Middle East and South America.

Within the UK, Armstrong *et al* identified NAFLD to be the most common underlying aetiology in patients referred from primary care with abnormal liver function tests (LFTs) with 7.6% of this population already having evidence of advanced fibrosis following further investigations[56]. Subsequently, NAFLD has recently been identified to be the second leading indication for a liver transplant with the expectation that it will soon become the main cause [57, 58].

In comparison to the general population, patients with NAFLD are not only at increased risk of liver related outcomes but they are also at increased risk of cardiovascular disease and death [59-63]. Ekstedt *et al* completed a prospective cohort study of 229 patients with biopsy proven NAFLD over a mean follow up period of 26.4 years and compared liver related outcomes and all-cause mortality to a reference population. The NAFLD patients not only had a significantly increased risk of mortality (HR 1.29, CI 1.04-1.59) but also a significantly increased risk of cardiovascular disease (HR 1.55, CI 1.11-2.15), hepatocellular carcinoma (HR 6.55, CI 2.14-20.03), infectious disease (HR 2.71, CI 1.02-7.26) and cirrhosis (HR 3.2, CI 1.05-9.81)[61]. Differentiating between NAFL and NASH has historically been thought to be of particular clinical importance because the majority of patients with simple steatosis will have a benign prognosis[59] whilst the 10-30% of patients with NAFL who progress to NASH have an increased risk of progressing to liver fibrosis and cirrhosis[64, 65]. However, recent evidence has suggested that even those patients with NAFL can progress to advanced liver fibrosis. McPherson *et al* identified 108 patients who had two liver biopsies more than 1 year apart and were diagnosed with NAFLD on their index liver biopsy. Of those patients with NAFL, 37% had progression of fibrosis on their second biopsy including 6 patients who had developed advanced (F3) fibrosis[66]. Recently, it has also been demonstrated that the fibrosis stage may in fact be more predictive of overall mortality than any underlying inflammation that is present. Ekstedt *et* al[61] reported that patients with a high NAFLD activity score (NAS) of 5-8 but only a minimal amount of fibrosis (F0-2) did not have an increase in overall mortality compared to the reference population (HR 1.41, CI 0.97-2.06) whereas patients with stage 3 or 4 fibrosis irrespective of the NAS score had an increased risk of mortality (HR 3.3, CI 2.27-4.76). Hagström et al[67] demonstrated that the risk of severe liver disease compared to a control group increased per stage of fibrosis (HR 1.9 in F0, 104.9 in F4) and adding in the presence of NASH did not significantly change these estimates. Subsequently, Dulai et al [68] demonstrated an increased risk of all-cause

mortality in patients with fibrosis compared to those without (F0) and also with each increase in stage of fibrosis. It could therefore be argued that use of early fibrosis in NAFLD as a risk stratification point would be of clinical benefit to not only reduce liver related mortality but also with the aim of reducing all-cause mortality. This cohort of patients could profit from further intervention and closer follow up by preventing complications of other associated metabolic co-morbidities e.g. type 2 diabetes and cardiovascular disease.

1.2.2.2 Risk factors

The increasing prevalence and escalating burden of NAFLD is driven by the vast numbers of patients with metabolic comorbidities in our society, predominately obesity and type 2 diabetes. Younossi *et al* [55] reported the that these comorbidities were associated with NAFLD in 51.34% and 22.51% cases respectively.

In 2013, 2.1 billion individuals worldwide were reported to be overweight or obese [69] which has far reaching consequences for the health service and wider society. Obesity is largely preventable and an unhealthy diet is now the leading factor driving poor health in the UK causing 10.8% of illness, in comparison to the 10.7% caused by smoking[70]. In England, 27% of the adult population are now reported to be obese (BMI≥30 kg/m^2) with estimates that this will rise to 45% by 2030[39, 71, 72]. Whilst Public Health England have reported that nearly two thirds of the adult population (64%) are either overweight or obese (BMI≥25 kg/m^2). In children the situation is just as grave with 19% of all children aged 10-11 years reported to be obese. An extrapolation of these figures have suggested that up to 500,000 children may already be at risk of developing liver disease[39].

Diabetes was reported to affect 382 million people worldwide in 2012 with estimates that this would increase to 592 million people by 2035[73]. In the UK, 6% of the population have a diagnosis of type 2 diabetes with estimates that a million more people remain undiagnosed in the general population [74].

1.2.2.3 Societal impact

Younossi et al [75] estimated 52 million people to have NAFLD within four European countries (Germany, France, Italy and the UK) with an annual cost of €35 billion or €354 to €1,163 per patient. The costs were calculated to be higher for those aged between 45-65 years of age and rose when societal costs were included.

For people who are overweight or obese the direct cost to the NHS has been estimated to be £6.1 billion[76] and spending on obesity related conditions has soared 65% in 10 years to £1.027 billion per year[36]. In 2016, the cost of obesity on the wider economy which includes social care, lost work productivity and welfare has been estimated to be £27 billion with estimates as high as £46 billion. For diabetes, approximately £10bn of the NHS budget is spent on its management with 80% of this allocated to the associated complications e.g. diabetic retinopathy, neuropathy and chronic renal failure[77]. A further £13.9bn has been estimated to be used for the indirect or non-health service costs of the disease.

1.3 Limitations of current diagnostic tests

The current diagnostic tests available to clinicians have significant limitations to be able to identify patients who may have early signs of chronic liver disease and are discussed further in this section.

1.3.1 Liver function tests

Liver function tests, commonly known as LFTs, include a group of enzymes which demonstrate abnormalities in the liver's biochemistry the results of which are commonly used to initiate a patient's referral to secondary care. The liver enzymes, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are released in response to liver cell damage, whilst alkaline phosphatase (ALP) is a marker of cholestasis. Whilst these enzymes are commonly collated together and reported within the panel of results for liver "function" tests (LFTs) they do not give a true representation of the performance of the liver. Bilirubin, albumin, international normalised ratio (INR) and the platelet count are more sensitive markers to demonstrate this.

However, current diagnostic pathways used within primary care to identify chronic liver disease are based upon abnormalities of these liver enzymes commonly referred to as liver function tests (LFTs). This strategy is flawed as abnormalities of ALT or AST are insensitive in detecting disease and these tests are often completed opportunistically. Mclernon *et al* [78] reviewed 95,977 patients from Tayside, Scotland, who had LFTs completed in primary care and identified 21.7% who had at least one abnormal LFT; after a median follow up of 3.7 years only 1.15% developed liver disease. Of those who are diagnosed with liver disease a significant proportion of patients have alanine transaminase (ALT) levels within the normal range (men <40 IU/L and women <31 IU/L) and would not necessarily be identified by current standard practice[79, 80]. Browning *et al* [49] reported 79% of the subjects in his study who were identified to have hepatic steatosis by proton magnetic resonance spectroscopy had a normal ALT level. Similarly, Fracanzani *et al[81]* reviewed the histological data of 458 patients in whom a liver biopsy was indicated and reported that in patients who had a normal ALT level 59% had features of NASH.

Conversely, if a patient is identified to have a raised ALT this does also not always signify underlying pathology and may cause patients to be referred for several unnecessary and costly investigations. Skelly *et al* reviewed the histology of 354 patients who underwent a liver biopsy and had abnormal liver functions tests; 73.7% of the biopsies reviewed did not have any evidence of liver fibrosis[82]. Likewise, a prospective cohort study which recruited 1118 primary care patients with incidental abnormal LFTs found no cause after further investigations in 45% of the cohort and subsequently 20% of this group were found to have normal LFTs on repeat testing[56].

However, while the British Society of Gastroenterology (BSG) guidelines[80, 83] advise GPs to refer patients with persistently abnormal LFTs to secondary care there continues to be a large variation in clinical practice. Results from the retrospective cohort study by Mclernon *et al* demonstrated that only 22.9% of the patients were referred once they were identified to have abnormal LFTs and only a further 4.7% of patients were referred after they had their LFTs repeated[84].

Liver function tests are also of limited use to monitor disease progression as the ALT level may decrease as liver fibrosis progresses to cirrhosis [85, 86]; potentially giving the clinician false reassurance. The absolute value of the ALT does not correlate with the underlying histological findings and therefore cannot be relied upon to diagnose liver disease at a specific time point within the natural history or be used to monitor any progression of disease over time[87]. Subsequently, Prati *et al* [88] attempted to improve the sensitivity of ALT by analysing blood results from 6835 first time blood donors and completing a

multivariate analysis. A new upper limit of normal for ALT was computed from the population at lowest risk of liver disease and was reported to be 30 U/L for men and 19 U/L for women, lower than the more commonly used cut offs of 40 U/L for men and 31 U/L for women. These updated values were shown to improve the sensitivity of ALT compared to previous cut offs (76.3% vs 55%) but reduced the specificity (88.5% vs 97.4%). However, when applied to an obese cohort of 233 women undergoing laparoscopic gastric bypass surgery who all had intraoperative liver biopsies the patients reclassified with abnormal LFTs were mainly identified to have fatty liver. The specificity for NASH or isolated portal fibrosis also decreased with the new cut off and could therefore lead to more patients undergoing unnecessary investigations[89].

1.3.2 Ultrasound

An abdominal ultrasound is a common investigation requested by general practitioners to investigate abnormal liver function tests and can be a useful diagnostic tool to identify solitary masses within the liver, gallstones as the cause of cholestatic LFTs, hepatic steatosis or features of cirrhosis and portal hypertension. It also has the advantages of being safe, readily available and inexpensive.

Hepatic steatosis can be easily recognised on ultrasound by causing an increase in echogenicity. However, the sensitivity of diagnosing hepatic steatosis is modest particularly when the amount of steatosis in the liver is low; once hepatic steatosis reaches 33% the sensitivity greatly improves[90]. Hepatic steatosis also decreases as liver fibrosis progresses to cirrhosis and is thus why past cases of cryptogenic cirrhosis are now thought to have been examples of burnt out NASH. Steatosis often co-exists with liver fibrosis and ultrasound is

not effective in differentiating between the two histological features. In fact, earlier stages of fibrosis (F0-2) in the absence of steatosis may not yield any changes that would be identified on ultrasound[91] and therefore its use in staging liver fibrosis is futile. Ultrasonography is also operator dependent and it can therefore also suffer from intraobserver and interobserver variability.

If positive features of cirrhosis are able to be identified on ultrasound for instance a nodular shrunken liver, an enlarged caudate lobe or signs of portal pressure including splenomegaly then it can become a highly specific tool. However, it has been demonstrated to have poor sensitivity in diagnosing liver cirrhosis. Martin *et al* completed a retrospective cohort study and compared the ultrasonography features in 342 cases with the histological diagnosis. The reporting of a nodular shrunken liver on ultrasound as a sign of cirrhosis had a sensitivity of 67.8% whilst the specificity was 87.5%[92].

1.3.3 Liver biopsy

For those patients who are identified to be at risk of chronic liver disease a liver biopsy may be required as it is the only diagnostic tool which allows the direct assessment of hepatocellular injury, inflammation and fibrosis and has therefore been considered to be the gold standard investigation for which every other non-invasive test is compared against. However, it does have several limitations.

A liver biopsy is an invasive procedure which can be completed either percutaneously or via the transjugular route. The procedure is also not without significant risk of complications; 10-30% of patients report pain[93, 94] and significant bleeding is identified in 0.4%[94]. As

with any invasive procedure there is also a small risk of death[94]. Data from the UK using Hospital Episode Statistics identified 61,187 patients who underwent a liver biopsy between 1998 and 2005[95]. The overall all-cause mortality at 7 days was found to be 0.2% with rates higher in those identified to have underlying malignancy. A sub analysis which only looked at day case patients referred for further investigation of liver disease or abnormal LFTs identified the 7 day mortality rate to be much lower at 1 in 10,000. The transjugular route is associated with a slight reduction in procedural complications and has the added benefit of being able to provide prognostic information by measuring the hepatic venous pressure gradient. It can also be completed in patients with contraindications to the percutaneous approach e.g. ascites, significant coagulopathy. However, this can only be completed in specialist centres and samples are often smaller with fewer portal tracts detected[96]. Nevertheless, a liver biopsy by either route requires an admission to a day case unit due to the risks of the procedure and the necessity for a period of observation (4-6 hours). This comes at an expense of £546.02 according to NHS reference costs[97].

The value of the histological analysis of a liver biopsy is also limited by the inter-observer and intra-observer variability along with the categorical variables used to describe a continuous process, as previously described[3]. Liver fibrosis is also not always homogenously distributed and considering a biopsy specimen only represents 1/50,000th of the liver this offers the potential for a significant sampling error to occur. Ratzui *et al*[98] reviewed paired biopsy samples from 51 patients with NAFLD; both samples were collected on the same day. No histological features displayed a high amount of agreement between the two samples and the discordance of one fibrosis stage or more was observed in 41% of the paired samples.

1.4 The rationale for changing current clinical practice

1.4.1 Chronic liver disease as a public health priority

In the UK, chronic liver disease is now identified to be a public health priority[27] with three independent reports including the Chief Medical Officer's annual report (2012)[99], the All-Party Parliamentary Hepatology Group Inquiry (2014)[25] and the annual reports from the Lancet commission (2014-2017)[22] [33, 57] highlighting concerns about the lack of concerted action taken to tackle the increasing rates of liver disease and the necessity for urgent action to be taken to address this issue. Yet despite these publications highlighting this impact there has been limited success of employing public health strategies to reverse this trend [100].

One notable success has been seen with minimum unit pricing for alcohol which is due to be implemented in May 2018 in Scotland after a failed legal challenge by the Scotch Whisky Association[101]. Other countries have now reported intentions to review their own legislation. Once implemented minimum unit pricing is estimated to make savings of £1.1bn in total direct costs[36]. In April 2018 there has also been the recent introduction of the soft drinks industry levy within the UK which aims to encourage soft drinks companies to remove added sugar, promote diet drinks and reduce portion sizes[102]. However, other recommendations to reduce the effects of hazardous alcohol use, obesity and type 2 diabetes such as stronger regulation of alcohol marketing, a restriction on trading hours for off-licences, fiscal measures on foods high in sugar, salt and fat and a reduction in advertisement and supermarket promotions of junk food have so far failed to be implemented[36].

Along with these recommendations on public health policies, these high profile reports have also highlighted the necessity of earlier detection and improved management of chronic liver disease within primary care. The most recent report from the Lancet commission commented on the lower than expected diagnoses of chronic liver disease compared to the expected prevalence within the general population after 1.5 million primary care records were analysed[57]. Two reasons for this were thought to be the time pressures on GPs and the limited documentation of risk factors; only 45.3% of patients had a documented record of their alcohol consumption within the past 5 years. Without first identifying those at risk the opportunity to further investigate for undiagnosed chronic liver disease will be missed. Furthermore, for those who are identified to be at risk the current tools and diagnostic pathways available to GPs, as previously discussed, are not fit for purpose and could result in a missed diagnosis.

1.4.2 An opportunity to implement new diagnostic pathways

As discussed, diagnosing and stratifying liver disease at an early stage is challenging due to the protracted natural history, the lack of symptoms even if the patient has underlying cirrhosis and the inadequacy of current diagnostic tests to identify patients who may have chronic liver disease. Consequently nearly half of patients are diagnosed during an emergency admission to hospital when signs of decompensation may already be present.

To date, it has not been recommended to screen the general population for evidence of chronic liver disease, although the value of targeting and risk stratifying specific populations has been debated [27, 103]. For NAFLD, the current practice guidelines by the American and European associations for the study of Liver disease do not advocate routine screening with

conflicting advice about which patients to have a high index of suspicion of advance disease and the best tool to diagnose these patients[104],[105]. For those patients at risk of ALD neither the American or European guidelines explicitly recommend screening for advanced fibrosis [29, 31].

However, with the development of several new non-invasive tests for liver fibrosis there is now the opportunity to modernise diagnostic pathways for chronic liver disease within primary care so that patients can be actively identified, reliably and accurately risk stratified and then referred on for more specialist input from a hepatologist if deemed appropriate. Providing a timely diagnosis for patients with advanced fibrosis or asymptomatic compensated cirrhosis is clinically important as lifestyle advice can be implemented early in an aim to slow the progression of disease, variceal and hepatocellular carcinoma surveillance can be organised and a referral for a liver transplant can be carefully planned. In addition, once anti-fibrotic treatments are developed the accurate diagnosis of the fibrosis stage will also influence when treatment should be commenced to reduce or stop the progression of disease. The non-invasive nature of these tests will also allow regular and repeated measurements to be undertaken to assess the response and provide information on future prognosis[106, 107], a weakness of current clinical practice in which liver biopsies are relied upon and utilised prudently due to the limitations previously discussed.

1.5 New non-invasive diagnostic tests for liver fibrosis

Developing non-invasive tests to diagnose and stratify chronic liver disease is challenging. A non-invasive test should have the characteristics of being able to objectively measure and evaluate a particular indicator of the normal biological process, the disease state or the

response to a pharmacological intervention[108]. Along with the obvious advantage of being more acceptable to the patient with a reduction in the risks and complications when compared to the alternative of a liver biopsy, non-invasive tests also offer the advantages of serial measurements and a potential reduction of costs to the health economy.

This section will provide a summary of the range of non-invasive tests which have been developed to diagnose liver fibrosis starting with a more detailed description of transient elastography and the Enhanced Liver Fibrosis (ELF) score which are discussed more extensively throughout the rest of the thesis.

1.5.1 Transient elastography

Transient elastography is a non-invasive diagnostic test which is performed using an ultrasound transducer probe (M probe). The probe transmits a vibration of low frequency (50Hz) which induces an elastic shear wave which propagates through the liver. This is followed by pulse echo ultrasound which allows the velocity of the shear wave to be calculated and is subsequently converted in to a liver stiffness measurement which is recorded in kilopascals (kPa). The harder or more fibrotic the tissue, the faster the shear wave will propagate through the liver and the greater the liver stiffness measurement [109]. The liver stiffness is measured within a volume of tissue measuring 1cm wide and 4cm in length starting at 25mm below the skin surface. This volume is approximately 100x larger than that of a biopsy sample and therefore more representative of the liver parenchyma.

The ability of transient elastography to quantify liver fibrosis was first reported by Sandrin *et al* in 2003 [109]. One hundred and six patients with chronic hepatitis C were evaluated and

the measurements were shown to be reproducible and well correlated to the grade of fibrosis. The areas under the receiver operating curve (AUROC) were 0.88 for the diagnosis of significant fibrosis (≥F2 fibrosis) and 0.99 for cirrhosis (F4 fibrosis). Subsequently, multiple studies have reproduced these findings in all major aetiologies of chronic liver disease and the correlation between stages of liver fibrosis has been extensively validated[110].

The initial reliability criteria set out by the manufacturer included the attainment of ten or more valid measurements with a success rate of ≥ 60% and an interquartile range/ median (IQR/M) ≤ 30%. Subsequent work has been completed to improve the reliability criteria [111]. Boursier *et al* [111] evaluated the liver stiffness measurements of 1,165 patients with chronic liver disease who had also had a liver biopsy. According to the original definition 75.7% of readings were reliable but the accuracy for the diagnosis of cirrhosis was not significantly different between the reliable and unreliable readings (85.8% vs 81.5%, p=0.082). A multivariate analysis demonstrated that the median reading and the IQR/M were independent predictors of fibrosis staging with the number of valid measurements or the success rate having no significant influence[111]. Thus three new reliability categories have been defined by Boursier *et al* [111]: very reliable (IQR/M ≤0.1); reliable (0.10<IQR/M ≤0.30, or IQR/M >0.3 with liver stiffness measurement <7.1kPa) and poorly reliable (IQR/M >0.3 and liver stiffness measurement median ≥7.1 kPa). Subsequently, 9.1% of liver stiffness measurements in the study's cohort were defined as poorly reliable versus 24.3% using the original criteria. The new reliability criteria also demonstrated a significant difference in the diagnostic accuracy of identifying patients with cirrhosis; 90.4% in the 'very reliable' subgroup, 85.8% in the reliable subgroup and 69.5% in the poorly reliable subgroup ($p < 10^{-3}$).

Use of transient elastography as a risk stratification tool in the community is appealing secondary to its ease of use, reproducibility, diagnostic accuracy, provision of timely results and that it is non-invasive. Consequently, recent studies have focused on its use within this context[112],[113]. However, transient elastography is operator dependent and may not give accurate results in patients with central adiposity. This limitation has recently been improved with the development of the XL probe which allows the elastic shear wave to be transmitted deeper into the liver parenchyma and avoids falsely measuring the subcutaneous adipose tissue which could lead to an overestimation of liver stiffness. Consequently this can reduce test failures in obese patients [114]. However, transient elastography has also been demonstrated to give false positive results in patients with steatohepatitis, cholestasis, congestive cardiac failure and in those patients who continue to drink alcohol and thus may not be sensitive to only fibrotic disease within the liver[115-117].

1.5.2 Enhanced Liver Fibrosis (ELF) score

The Enhanced Liver Fibrosis (ELF) score is based on an algorithm calculated from three direct serum markers of the liver matrix metabolism which include tissue inhibitor matrix metalloproteinase 1 (TIMP1), hyaluronic acid (HA) and terminal peptide of procollagen III (PIIINP). The algorithm, which originally also included age, was initially reported by Rosenberg *et al*[118] and was derived and validated in a cohort of 921 patients with mixed aetiologies of chronic liver disease. The sensitivity of the original ELF score to detect stage 3 or 4 fibrosis was reported to be 90% with a negative predictive value of 92% and an AUROC of 0.804. The ELF score has subsequently been validated in specific patient cohorts. Guha *et al* [119] evaluated the ELF score in 196 patients with NAFLD and reported an AUROC of 0.9 for identifying fibrosis stages 3 and 4. Similarly in a cohort 347 of patients with hepatitis C, Parkes *et al* reported an AUROC of 0.85 to detect severe liver fibrosis (stages 3/4) [120]. The

ELF score has also been demonstrated to predict future clinical outcomes. In a cohort study of 457 patients with mixed aetiology of chronic liver disease those with a high ELF score were significantly more likely (hazard ratio = 75) to have a liver related outcome compared to those with the lowest scores[121]. A unit change in the ELF score was also shown to double the risk of a liver related outcome.

1.5.3 Summary of other non-invasive tests

1.5.3.1 Indirect serum markers

Indirect serum markers reflect hepatic dysfunction due to underlying fibrosis +/- portal hypertension and are created from simple blood tests and physiological parameters which can be routinely measured within clinical practice. These simple panels are attractive as they are economical, have known reproducibility and have the potential to be collected as part of routine practice. The published data suggests that simple panels such as the AST:ALT ratio, FIB-4 score, the NAFLD fibrosis score and the BARD score are able to accurately identify those patients without advanced fibrosis or cirrhosis in NAFLD (Table 1.1)[122]. However, they are of limited use in distinguishing between milder stages of fibrotic disease (F0-2) or in identifying patients with steatohepatitis. The majority of these simple panels are also restricted for use within a specific cohort of patients with only a few tests validated for more than one aetiology of liver disease (e.g. AST:ALT ratio, FIB-4). Therefore the underlying risk factor must be taken into consideration before identifying the most accurate indirect serum marker to be used.

Table 1.1: Examples of Indirect Serum markers to detect Advanced Fibrosis

Name	Formula and variables	Threshold	Sensitivity	Specificity	AUROC	Reference
BARD	BMI ≥ 28 = 1 point AST/ALT ratio ≥ 0.8 = 2 points T2DM = 1 point	Score ≥ 2	0.91	0.66	0.81	[123]
FIB-4	Age x AST (IU/L)/ platelet count ($x10^9$/L) x √ALT (IU/L)	>2.67 for advanced fibrosis <1.30 for absence of advanced fibrosis	0.33	0.98	0.80	[124]
			0.74	0.71		
AST:ALT ratio	AST (IU/L)/ALT (IU/L)	>1 in HCV cirrhosis >0.8 in NAFLD	0.53	1.0	0.83	[125]
			0.74	0.78		[122]
APRI	AST (IU/L)/(upper limit of normal/ platelet count ($x10^9$/L) x 100	>1	0.27	0.89	0.67	[122]
BAAT	Age ≥ 50 years BMI ≥ 28 TG ≥ 1.7 mmol/L ALT ≥ 2x ULN	All 4 parameters	0.14	1.0	0.86	[126]
NAFLD fibrosis score	-1.675 + 0.037 x age (years) + 0.094 x BMI(kg/m^2)+1.13 x diabetes (Yes = 1, No = 0)+0.99x AST/ALT ratio - 0.013x platelet ($x10^9$/L) - 0.66 x albumin (g/dl)	>0.676 for presence of significant fibrosis <-1.455 for absence of significant fibrosis	0.51	0.98	0.82-0.88	[127]
			0.82	0.77		

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUROC, area under the receiver operating characteristic curve; BMI, body mass index; HCV, Hepatitis C Virus; NAFLD, Non-alcoholic fatty liver disease; T2DM, Type 2 diabetes mellitus; TG, Triglycerides.

1.5.3.2 Direct serum markers

Direct serum markers (Table 1.2) reflect the changes of the extracellular matrix (ECM) or the breakdown products. While direct serum markers have been identified to be accurate in diagnosing significant disease they are also less reliable in identifying individual stages of fibrosis [128]. It is also unclear if the ECM products which are being measured are specific to the fibrosis progression and regression that is occurring within the liver and if they are sensitive enough to detect small changes in histological improvement. Moreover, questions remain about the effect of extra-hepatic fibrosis on these markers. Direct serum markers can also be more expensive to perform as the Enhanced liver fibrosis score (ELF) [119] and Fibrotest[129] are commercial panels requiring additional assays and are therefore sent to an external lab for analysis. However, this is now changing with the ELF score now available within some NHS trusts.

1.5.3.3 Imaging based modalities

Imaging based modalities such as ultrasonography have been used for several decades to diagnose liver disease but as previously discussed are not very sensitive. Newer techniques (Table 1.3) have been developed using existing technologies to overcome this current limitation.

Table 1.2: Examples of direct serum markers

Name	Formula and variables	Threshold	Sensitivity	Specificity	AUROC	Reference
PIIINP	Terminal peptide of procollagen III	>6ng/ml. Discriminates simple steatosis from NASH	0.66	0.80	0.83	[130]
ELF	2.494 + 0.846 $\ln(C_{HA})$ + 0.735 $\ln(C_{PIIINP})$ + 0.391 $\ln(C_{TIMP1})$	>0.3576	0.80	0.90	0.90 for ≥ F3 fibrosis	[119]
Fibrotest	Patented algorithm including total bilirubin, GGT, A2M, ApoA1 and Haptoglobin. Correct for age and gender	>0.715	0.79	0.96	0.81 for ≥ F2 Fibrosis	[129]

A2M, α2-macroglobulin; ApoA1, apolipoprotein A-1; AUROC, area under the receiver operating characteristic curve; ELF, Enhanced Liver fibrosis score GGT, gamma-glutamyltransferase; HA, hyaluronic acid; NASH, non-alcoholic steatohepatitis; PIIINP, procollagen III; TIMP1, tissue inhibitor of matrix metalloproteinase 1.

Table 1.3: Imaging based modalities

Name	Measurement	Sensitivity	Specificity	AUROC	Reference
MR elastography (MRE)	-Liver fibrosis -Discriminating steatosis from NASH	0.94	0.95	0.98 for ≥F2 fibrosis	[131]
		0.94	0.73	0.93	[132]
Transient elastography (TE)	Hepatic elasticity correlates with the degree of liver fibrosis	0.91	0.75	0.89 for ≥F3 fibrosis	[110]
Acoustic radiation force impulse (ARFI)	An increase in the median velocity with increasing severity of liver fibrosis	0.80	0.85	0.898 for ≥ F3 fibrosis	[133]

AUROC, area under the receiver operating characteristic curve; NASH, non-alcoholic steatohepatitis; kPa, kilopascal.

One main advantage of using imaging based modalities is that they are organ specific and the results can easily be reproduced. Acoustic radiation force impulse (ARFI) provides an estimate of liver stiffness in shear wave speed (m/s) and uses a conventional ultrasound scanner so can therefore be completed at the same examination as the hepatic parenchyma. However, it has the same limitation as transient elastography and shows increased variability in those who are obese. At present the data and experience of using ARFI is limited although the diagnostic performance is similar to transient elastography [133, 134].

New techniques using magnetic resonance imaging (MRI) have been developed which allow the quantification of inflammation and steatosis and which have also been demonstrated to have a high diagnostic accuracy for staging liver fibrosis[131, 135]. MRI imaging techniques, such as MRE, are less influenced by subcutaneous fat and operator variability and have also been validated within different aetiologies of liver disease [135]. However, they have their own challenges, including the requirement of additional hardware and compatibility across different MR platforms. This is an area of rapid development and novel protocols which require no additional contrast or hardware have begun to emerge [136, 137].

1.5.3.4 Diagnostic accuracy of non-invasive tests

For a non-invasive test to be a useful stratification tool its performance must be diagnostically accurate. This is assessed by calculating the area under the receiving operator curve (AUROC) which plots the sensitivity of a test against (1-specificity) at different thresholds. A value of 1.0 represents a perfect diagnostic test while a value of 0.9 is excellent and a value of 0.8 is good. A value of 0.5 implies that the result of the test could have occurred by chance alone. The imaging based modalities have all been demonstrated to be

excellent diagnostic tests when being used to identify patients who may have advanced disease (F3) or cirrhosis (F4). Friedrich-Rust *et al* completed a meta-analysis to analyse the diagnostic performance of transient elastography across all aetiologies including NAFLD and ALD. Thirty five studies were included in the analysis for the diagnosis of severe fibrosis (≥F3) and a mean AUROC of 0.89 (95% CI, 0.88-0.91) was reported[110]. The diagnostic accuracy decreased when used to diagnose milder forms of fibrotic injury although when compared to direct and indirect serological markers (Table 1.4) they still perform remarkably well.

Table 1.4: The diagnostic accuracy of selected non-invasive tests for different stages of fibrosis

Non-invasive test	**Disease**	**AUROC**			**Reference**
		≥F2	**≥F3**	**≥F4**	
ELF	HCV/HBV/ PBC	0.78	-	0.92	[138]
Fibrotest	HCV/HBV/ PBC	0.69	-	0.91	[138]
BARD score	NAFLD	-	0.81	-	[123]
Transient elastography	Mixed	0.84	0.89	0.94	[110]
MR elastography	Mixed	0.88	0.93	0.92	[135]

AUROC, area under the receiver operating characteristic curve; HBV, Hepatitis B virus; HCV, Hepatitis C virus; PBC, Primary biliary cirrhosis.

Non-invasive tests can also accurately identify patients at low risk of significant disease and thus avoid the need for this cohort of patients to undergo further investigations which may be invasive. Simple panel markers such as the AST:ALT ratio, FIB-4 score, NAFLD fibrosis score (NFS) and the BARD score have been used in patients with NAFLD and have been demonstrated to have a negative predictive value of greater than 90% and can therefore be used to reliably exclude advanced fibrosis and cirrhosis[122]. Similarly, transient

elastography has been demonstrated to have excellent negative predictive values however, this does depend on the liver stiffness cut off that is used, the fibrosis stage that is being detected and the underlying aetiology. Wong *et al* analysed transient elastography results against liver biopsy specimens of 246 patients with NAFLD and reported that a negative predictive value for ≥F3 disease of 92.6% if a cut off value of 9.6 kPa was used[139]. If the liver stiffness cut off was reduced the negative predictive value further improved; a cut off of 7.9kPa generated a negative predictive value of 96.6%. Nguyen-Khac *et al* completed a similar study in 103 patients with hazardous alcohol use and identified a negative predictive value of 84.3% when using a liver stiffness cut off of 11kPa to identify patients with ≥F3 disease[140].

1.5.3.5 Validation of non-invasive tests in a community setting

The majority of evidence for the use of non-invasive tests are still derived and validated from populations based within secondary care [110, 123, 127]. Thus extrapolation of these tests to a cohort in the community may not be valid due to a lower prevalence of disease, a reliance upon abnormal LFTs which pre-selected the original cohorts and a variation in the performance of the test within a different population, known as the spectrum effect [141, 142]. Hence, there remains an unmet need to identify which non-invasive tests have been successfully utilised and validated within this alternative health care setting.

1.6 Aims

Using an inexpensive and accurate non-invasive test for liver fibrosis in a primary care setting would allow a large number of patients to be stratified for their risk of chronic liver disease and identify those who would benefit from a referral to specialist services or further

follow up in secondary care. However, further research is required to determine the optimal approach and whether this is cost effective. In this thesis, I aim to:

1. Complete a systematic review of the non-invasive tests for liver fibrosis which have been used to stratify patients at risk of ALD and NAFLD in the community and determine which tests are validated within a general population setting.
2. Characterise the risk of clinically significant liver disease assessed by a non-invasive test within subpopulations of a community who are stratified based on their underlying risk factor(s). In particular, the significance of a BMI ≥27.5kg/m^2 as a risk factor for chronic liver disease will be analysed.
3. Analyse the performance of the non-invasive test within a subpopulation who are overweight.
4. Complete an economic evaluation to investigate the cost effectiveness of implementing a risk stratification pathway which targets patients at risk of chronic liver disease compared with current standard of care.

2 A systematic review of the use of non-invasive tests in a community setting to stratify for alcoholic and non-alcoholic fatty liver disease

2.1 Chapter summary

At present, there is no evidenced based pathway to stratify risk of chronic liver disease in a community setting. This chapter presents the results of a systematic review of non-invasive tests used to stratify patients at risk of alcoholic and non-alcoholic fatty liver disease in the community and report the prevalence of chronic liver disease as defined by these tests. The prevalence of advanced liver fibrosis and cirrhosis in the general population was identified to be between 0.9%-2% and 0.1%-1.7% respectively. Studies targeting patients with risk factors for liver disease (e.g. hazardous alcohol use or type 2 diabetes) reported a higher prevalence of advanced liver fibrosis (0%-27.9%) and cirrhosis (2.4%-4%). There is a significant burden of chronic liver disease in the community which is currently undetected, however an optimal strategy for risk stratification is not yet clear.

2.2 Introduction

The introduction of this thesis outlined the increasing health burden that chronic liver disease has become worldwide which, in 2015, accounted for 2% of all deaths and 1.2% of disability adjusted life years[17, 18, 143]. Increasing mortality rates are attributable to viral

hepatitis but also driven by the increasing prevalence of adverse lifestyle related risk factors which have resulted in alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) becoming the most common causes of chronic liver disease in the Western world[20, 21, 27].

Due to the increasing morbidity and mortality of chronic liver disease there is a necessity for urgent action to be taken to prioritise the earlier identification and treatment of patients, particularly within the community[33]. As previously outlined, commonly used diagnostic tests have poor sensitivity and specificity, are completed opportunistically or are not appropriate to be used within a community setting. Liver function tests (LFTs) in particular are inappropriately relied upon by primary care physicians to identify patients with asymptomatic chronic liver disease [78, 82, 87].

At present, an evidenced based risk stratification pathway does not exist within a community setting to screen the general or a targeted population who are at risk of chronic liver disease. Until recently a barrier has been the absence of a robust and reproducible screening tool. With the advent of non-invasive tests of liver fibrosis this is now a possibility. However, the majority of evidence has been derived and validated from populations based within secondary care [110, 123, 127] and thus extrapolation of these tests to a cohort in the community may not be valid due to a reliance upon abnormal LFTs instigating referral for specialist advice, a different prevalence of disease and spectrum bias.

To facilitate the emergence of strategies which aim to risk stratify patients in the community we have systematically reviewed the available evidence. From this, the scale of undiagnosed

chronic liver disease can be determined, the inadequacy of current referral pathways can be highlighted and an optimal risk stratification strategy potentially proposed. As the commonest causes of chronic liver disease are ALD and NAFLD we have focussed on the non-invasive tests which have been used to stratify patients at risk of these aetiologies.

2.3 Aims

The aims of this systematic review were:

a) To determine the proportion of the studied populations found to have clinically significant liver disease as defined by the non-invasive tests used in the individual studies.
b) To identify the proportion of patients with liver fibrosis or cirrhosis as defined by the non-invasive test who had normal ALT results.
c) To evaluate the difference in the proportion of patients identified as having liver disease using non-invasive tests between unselected or targeted populations within a community setting.
d) To determine the patient variables which are significant in identifying patients with liver fibrosis

2.4 Methods

This review was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions[144] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[145]. The study identification, data collection and subsequent analysis was performed in conjunction with a second research fellow Dr David Harman (DH; Clinical research Fellow in Hepatology, Nottingham Digestive Diseases Biomedical Research Centre).

2.4.1 Search strategy

A structured search algorithm for identification of studies to be considered for inclusion with the systematic review was created following the PICO question structure:

Participants – Unselected adults or adults identified to have a risk factor for non-alcoholic fatty liver disease (NAFLD) or alcoholic Liver disease (ALD) based within a general population setting.

Intervention – Non-invasive test for liver fibrosis

Comparison – Histopathology from a liver biopsy. Although this was not an absolute requirement as detailed below.

Outcome – Prevalence of liver fibrosis or cirrhosis as defined by the non-invasive test which was used.

Key MeSH headings and free text search terms were defined relevant to the participants involved in the studies, the two aetiologies of chronic liver disease, the community setting and the non-invasive tests used to stratify for liver fibrosis. Subsequently, a search algorithm

was derived in collaboration with a local librarian (Alison Ashmore; University of Nottingham). The final search algorithms including the MeSH terms used within the specific electronic databases are listed within the Appendix (Section 7.1). Two independent searches of EMBASE (January 1980 to January 2015), MEDLINE (January 1946 to January 2015) and Web of Science were completed. Additionally a hand search was completed of all major UK and worldwide conference proceedings dating back to 2010 including the British Society of Gastroenterology (BSG), the British Association for the Study of Liver Disease (BASL), the European Association for the Study of Liver Disease (EASL) and the American Association for the Study of Liver Disease (AASLD). A targeted search was also completed of reference lists from the original studies and abstracts including any review articles or citations that were identified.

Identification of studies was commenced in November 2014 and completed in January 2015. The titles and abstracts of all studies identified within the literature search were screened to determine their suitability for inclusion within the review. The full texts of all studies considered to be suitable were assessed for eligibility.

2.4.2 Selection criteria

Listed below are the eligibility criteria used to screen the individual studies for inclusion within the review.

Studies were included if:

- The study was performed in adults defined as 18 years or older

- The study population was from a non-hospital setting e.g. community, primary care or outreach unit
- Study participants underwent a validated non-invasive test which would stratify for liver fibrosis.
- The prevalence of clinically significant liver disease, either liver fibrosis or cirrhosis was reported as an outcome measure by the study. Validation of the result by histopathology was not an absolute requirement.
- Participants were recruited from an unselected population or based upon the participants age or a defined risk factor for ALD or NAFLD

Studies were excluded if:

- Data regarding the study population, the setting in which the non-invasive test was completed or the threshold for the non-invasive test was not adequately reported.
- Participants were solely investigated for non-ALD or non-NAFLD related liver disease e.g. viral hepatitis
- They were not published in the English language

2.4.3 Data collection

Data extraction was completed and recorded by the two researchers (RH/DH) independently within a predefined table and reviewed for any discrepancies. Any disagreements were discussed but if these could not be resolved the advice from a third reviewer (Dr Indra Neil Guha; Clinical Associate Professor, University of Nottingham) was sought.

The data extracted from each study included:

1. Study characteristics – First Author, study location, details of patient selection and screening uptake
2. Details of the patient population – Age, gender, prevalence of liver disease risk factors
3. Details of the non-invasive test(s) and the diagnostic cut off(s) which were used
4. Details of the outcome measure – The reported prevalence of liver fibrosis and/or cirrhosis within the population studied as defined by the non-invasive test which was used. Details of validation with histological findings (if a liver biopsy was performed) and the percentage of normal alanine aminotransferase (ALT) levels in patients reported to have an abnormal non-invasive test result.

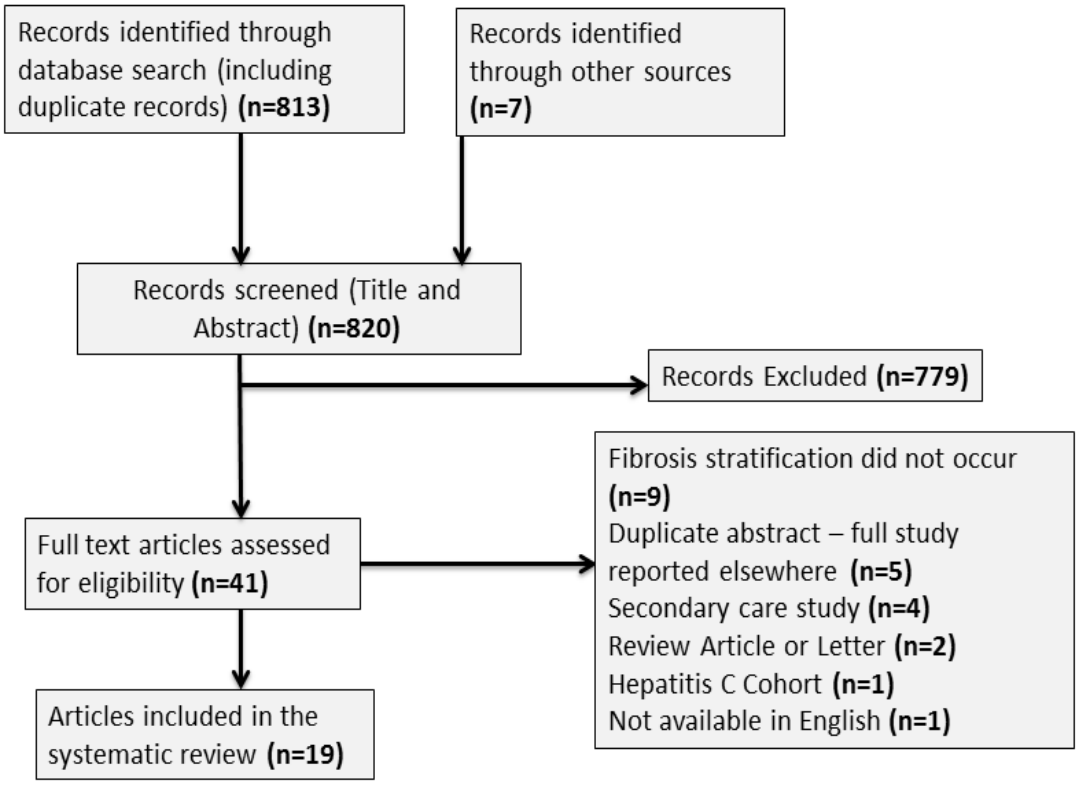
2.4.4 Outcome measure

The outcome measure varied between studies with the prevalence of any, significant, advanced liver fibrosis and/or cirrhosis reported. As previously discussed in the introduction of this thesis, several semi-quantitative histological scoring systems exist depending on the underlying aetiology [3, 4] and largely these divide the spectrum of liver fibrosis into four categories (F1-F4). Subsequently the outcome measures reported within this systematic review coincide with the following terminology: ≥F1 stage = any liver fibrosis, ≥F2 stage = significant liver fibrosis, ≥F3 stage = advanced liver fibrosis and F4 stage = cirrhosis.

2.4.5 Meta-analysis

Due to the lack of comparable studies and substantial heterogeneity a meta-analysis could not be performed.

Figure 2.1: Flow diagram of the article search strategy and selection of studies eligible for data analysis



2.5 Results

Our systematic search of bibliographic databases identified a total of 813 citations. An additional 7 studies were identified from the grey literature. Following screening of the titles and abstracts, a total of 779 studies were excluded. The full text of 41 studies was assessed against the inclusion and exclusion criteria resulting in a further 22 studies being excluded from the final analysis. Finally, 19 studies including 17 full journal articles and 2 abstracts were included within the systematic review. The overall results of the search strategy are presented in Figure 2.1.

2.5.1 Non-invasive tests used

Eleven different non-invasive tests were utilised to stratify patients for liver fibrosis. Transient elastography (TE) was the only imaging based modality and was the most frequently used test included within 12 out of the 19 studies identified. The remaining non-invasive tests were all serum based and comprised NAFLD fibrosis score (NFS), used within 5 studies, Fibrotest, used within 3, the BARD score, AST:ALT ratio, APRI score and the FIB4 index which were used within 2 and the BAAT score, Hyaluronic acid, the ELF score and the Southampton traffic light test which were all used once within separate studies. The baseline characteristics of individual studies including patient demographics are reported within Table 2.1.

2.5.2 Target population

There was significant heterogeneity in the community studies included for analysis (Table 2.1). The initial target population tested by the non-invasive tests varied. Five studies stratified the general population according to an age cut off whilst a further 5 studies

stratified an unselected group of adults. The prevalence of risk factors reported within these studies would be as expected for the general population apart from the study by You *et al*[146] in which the prevalence of type 2 diabetes was raised at 11.9%. Ten studies stratified patients with risk factors for NAFLD including 3 studies [147-149] which completed subgroup analysis on patients initially identified from the general population. Four studies stratified patients known to be at risk of ALD including 1 study by Baba *et al* [147] which had completed further subgroup analysis on unselected patients initially identified from an annual medical check-up at a community health centre. Heterogeneity also existed in the choice of non-invasive test and outcome measure, including the severity of liver fibrosis.

2.5.3 Screening uptake

The proportion of patients that participated in screening from the invited study population was reported in eight studies. This ranged from 20%-89% for the first study visit. The lowest uptake was observed in the studies by Williamson *et al* [150] and Morling *et al* [151] in which 5454 patients were randomly invited from the Lothian Diabetes Register with 1066 (20%) subsequently attending a baseline visit. Further study visits at 1 year and 4 years reported an attendance of 939 (88% of study cohort) and 831 (80% of study cohort) respectively. Whilst 8.2% of the original study cohort had died, 11.6% of participants were unable or unwilling to attend suggesting attrition with multiple study visits.

The highest uptake was reported by Das *et al* [152] which invited participants at random from a voting registry of the Nagari Gram Panchayat Village in India. A screening uptake of 89% was achieved. This appears to be an anomaly with the next highest screening uptake

reported by Moessner *et al* [113] (59% of the study cohort) in which participants were opportunistically recruited from a drug and alcohol outreach centre in Denmark.

In studies which had multiple steps within the algorithm [153, 154] a decline in uptake was observed. In the study by Sheron *et al* [153] a positive AUDIT questionnaire was recorded in 24.3%, however only 34.8% of this group subsequently attended clinic for the non-invasive test to be completed.

2.5.4 Prevalence of fibrosis

All 19 studies reported the prevalence of liver fibrosis according to a specified threshold for the non-invasive test which was utilised.

2.5.4.1 Unselected population

In those studies reporting unselected patients from the general population the prevalence of liver fibrosis ranged from 2%-19% (Table 2.2). All 5 studies utilised TE but the results varied due to the different liver stiffness thresholds that were chosen and the degree of liver fibrosis that was estimated. The lowest estimate obtained in the study by Wong *et al* [148] used the highest threshold of 9.6 kPa and estimated the prevalence of advanced liver fibrosis only. The highest estimate in the study by Malik *et al* [155], used a lower threshold of 7.0 kPa and estimated the prevalence for any liver fibrosis. In the 5 studies which stratified members of the general population according to an age cut off, the prevalence ranged from 0.7%-25.7%. The lowest estimate obtained in the study by Poynard *et al* [154] used a two-step approach with only half of the patients re-attending for the second test. Overall only two studies stratified members of the general population for advanced liver

fibrosis. The reported prevalence was 0.9% [156] and 2% [148] using Fibrotest ≥0.59 and TE ≥ 9.6 kPa respectively.

2.5.4.2 Non-alcoholic fatty liver disease

In the ten studies that stratified patients identified to be at risk of NAFLD the reported prevalence of liver fibrosis ranged from 0% - 92.6% (Table 2.3). Again, the prevalence varied dependent on the non-invasive test which was used and the degree of liver fibrosis that was being estimated. In the 5 studies that estimated any liver fibrosis the prevalence ranged between 0.4%-92.6%. The studies which reported the highest estimates of prevalence were Williamson *et al* [150] and Morling *et al* [151] in which 100% of the study population were reported to have type 2 diabetes. Four studies estimated the prevalence of advanced liver fibrosis which ranged from 0%-27.9%. The highest estimate was obtained from Vesey *et al* [149] who only recruited patients aged over 65 years, therefore increasing the probability of disease being identified. The lowest estimate was obtained in the study by Wong *et al* [148] who utilised several non-invasive tests to demonstrate the prevalence of advanced liver fibrosis. In this cohort, use of the NAFLD fibrosis score≥0.676 and APRI≥1.5 estimated a 0% prevalence for advanced fibrosis, while using TE≥9.6kPa and AST:ALT ratio≥1.0 the prevalence increased to 3.7% and 12.1% respectively.

2.5.4.3 Alcoholic liver disease

In the four studies that stratified patients identified to be at risk of ALD the reported prevalence ranged between 11%-20.5% (Table 2.4). In the three studies [113, 147, 157] which utilised TE the reported disease prevalence was similar despite two different thresholds being chosen and the reported outcome measures being different.

2.5.5 Prevalence of cirrhosis

Only seven studies reported the prevalence of cirrhosis which varied depending on the study population being stratified (Table 2.5). In the four studies that used subjects from the general population the reported prevalence varied between 0.1%-1.7%. The highest estimate was obtained by Malik *et al*[155] but they did not report the risk factor prevalence in the study population. It cannot therefore be determined why this self-selected group were at increased risk of having clinically significant liver disease. The other three studies which stratified patients due to an underlying risk factor reported a prevalence of 2.4%-4.0%; a much higher estimate of liver cirrhosis prevalence compared to studies of the general population. Interestingly, in the study by Das *et al* [152], which reported a cirrhosis prevalence of 2.4% in patients with NAFLD, the prevalence of cirrhosis in their unselected cohort was calculated to be 0.2%; equivalent to the estimates reported in the other studies of the general population.

2.5.6 Liver biopsy results

Only six studies utilised histology on liver biopsy to confirm the diagnosis of liver fibrosis/cirrhosis as indicated by the non-invasive test (Table 2.6). This includes 5 studies which used TE, all of which used different thresholds of liver stiffness, and 1 study which used Fibrotest. No study completed liver biopsies in all of the patients undergoing the non-invasive test.

Across the 6 studies, the acceptance rate of liver biopsies varied between 22.5%-87.5% with the lowest acceptance rates (22.5%-38.9%) seen in the sub groups of patients with a lower risk of advanced liver fibrosis or cirrhosis according to the non-invasive test threshold [112,

155, 157]. The acceptance rates were seemingly higher in those at a higher risk of advanced disease. In the study by Roulot *et al* [112] the acceptance rate was 100% in the 9 patients who had a liver stiffness reading >13kPa, all of whom were confirmed to have a histological diagnosis of cirrhosis. However, in comparison to the study by Moessner *et al* [113] who used a similar liver stiffness threshold of 12kPa, only 20/45 (44.4%) patients accepted a liver biopsy and only 9/20 (45%) were confirmed to have a histological diagnosis of cirrhosis. The other patients were identified to have varying degrees of liver fibrosis (4/20 = F1 fibrosis, 3/20 = F2 fibrosis, 4/20 = F3 fibrosis). Importantly, this cohort had an underlying risk factor of hazardous alcohol use for which a higher liver stiffness threshold is proposed to predict advanced fibrosis and cirrhosis compared to other aetiologies[140, 158].

2.5.7 ALT levels and predictors of significant liver disease

Nine studies have reported the percentage of patients with an abnormal test result who had normal ALT levels (Table 2.2, 3 and 4). This indicates the percentage of patients who would traditionally not have been identified though current referral algorithms which are based upon abnormal LFTs. Two studies by Wong *et al*[148] and Grattagliano *et al*[159] used conservative ALT levels of >19 IU/L for women and >30IU/L for men as suggested by Prati *et al*[88] whilst the remaining studies used the more traditional cut offs between 35 and 50 IU/L.

The percentage of patients with liver fibrosis who had a normal ALT level in the studies of the general population ranged from 40%-74.6% and in those which identified patients with an underlying risk factor ranged from 26.5%-87.5% respectively. The lowest estimates reported within both ranges were seen within the two studies which utilised the more

conservative cut offs. Of the three studies which used traditional cut offs in the patient populations with an underlying risk factor, 72.4%-87.5% of patients had a normal ALT level and would not have been routinely identified.

Harman *et al*[157] was the only study which reported the percentage of patients with a normal ALT level who were diagnosed with cirrhosis. In this study 90.9% of patients with asymptomatic compensated cirrhosis would not have been identified via traditional community based algorithms.

2.5.8 Predictors of clinically significant liver disease

Five studies completed a multivariate logistic regression analysis to identify the variables that independently predict an outcome of elevated liver stiffness using TE or significant/confirmed fibrosis from a non-invasive test result (Table 2.7). The key variables identified to have a significantly raised odds ratio (OR) include a raised BMI (OR: 1.487-3.25), an elevated waist circumference (OR: 1.05-1.9), an abnormal ALT (OR: 1.078-4.2), the age of the patient (OR: 1.08-1.8) and being male (OR: 6.36-6.74).

Table 2.1: Baseline characteristics of 19 studies. Listed in order of risk factor for liver disease (unselected general population, general population selected by age, NAFLD risk factors, ALD risk factors, risk factors for both NAFLD and ALD

Study (First Author)	Study Location/Patient Selection	Liver Disease Risk Factor	Non-invasive Test Utilised	Total Study Population	No. of Participants Screened	Mean Patient Age (years)	Male Gender (%)
Baba[147]	Japan; annual medical check-up at community health centre	Unselected; alcohol and NAFLD subgroup analyses	TE	Not Stated	423 (of whom valid TE in 416 (98.3%)); subgroups of alcohol misuse (n=151) and NAFLD (n=58)	47.4	60.1%
Wong[148]	Hong Kong; subjects invited at random aged 18-70 from census database	Unselected. Subgroup analysis of patients with NAFLD (MRS)	TE (all); NAFLD – AST:ALT ratio, APRI, BARD, FIB4, NAFLD fibrosis score	3000	922 (of whom valid TE in 759 (82.3%)) NAFLD subgroup - 264	48.0	42.2%
You[146]	South Korea; healthy subjects attending health check at local hospital	Unselected	TE	Not Stated	164 (of whom valid TE in 159 (97%))	56.0	54.7%
Lemoine[160]	The Gambia; community screening of healthy subjects	Unselected	TE	Not Stated	76 (of whom valid TE in 72 (94.7%)	49.5	43%
Malik[155]	United Kingdom; subjects recruited via advert and reviewed in private clinic	Unselected	TE	Not Stated	116	Not stated	Not stated

Fabrellas[161]	Spain; subjects invited at random from state health registry	Age 18-70 years	TE	Not Stated	502 (Of whom valid TE in 495 (98.6%)	47.2	41%
Zelber-Sagi[156]	Israel; random sample of participants of First Israeli National Health and Nutrition Survey	Age 25-64	Fibrotest	799	349 (of whom 338 (96.8%) had valid Fibrotest results)	50.8	54.7%
Poynard[154]	France; free medical check-up at community health centre	Age≥40 years	Fibrotest, TE	Not Stated	7,554 (of whom valid Fibrotest/absence of previous liver disease in 7,482 (99%))	56.9	55.1%
Roulot[112]	France; free medical check-up at community health centre	Age>45 years	TE	Not Stated	1,358 (of whom valid TE in 1,190 (87.6%))	57.7	60.5%
Veysey[149]	Australia; general population screening of elderly patients	Age ≥65 years	NAFLD Fibrosis Score	Not Stated	440; subgroup of 190 subjects with NAFLD (Fatty Liver Index)	78.0	40%
Armstrong[56]	United Kingdom; screening of subjects with raised ALT level from 8 primary care practices	NAFLD (ultrasound) and raised ALT	NAFLD Fibrosis Score (NFS)	Not Stated	295 (of whom NFS measured in 236 with available serum)	58.0	56.6%
Kim[162]	United States; subjects from NHANES III general population cohort (1988-1994)	NAFLD (ultrasound)	NAFLD Fibrosis Score	Not Stated	4,083	45.5	50.4%
Grattagliano[159]	Italy; subjects from 10 primary care practices	NAFLD (ultrasound)	Fibrotest	Not Stated	259	51.0	63.7%
Williamson[150]	Scotland; subjects from Lothian Type 2 Diabetes cohort (aged 60-74)	Type 2 Diabetes	Hyaluronic acid, BAAT, BARD, NAFLD fibrosis Score	5,454	939 (year 1 clinic attendees); subgroup of 663 with possible NAFLD	68.9	52%

Morling[151]	Scotland; subjects from Lothian Type 2 Diabetes cohort (aged 60-74)	Type 2 Diabetes; Subgroup analysis of patients with NAFLD (Ultrasound)	TE, ELF Score, AST:ALT ratio, APRI, FIB4	5,454	767 (year 4 clinic attendees); subgroup of 282 with NAFLD	71.4	52.8%
Das[152]	India; 1 in 3 sample of voting registry invited at random. Investigations both in	NAFLD (Ultrasound and CT) and raised ALT	TE	2,406	44 (out of 1,911 screened for NAFLD, 164 were positive and 44 also had raised ALT)	39.0	54%
Sheron[153]	United Kingdom; screening of subjects from 9 primary care practices	Alcohol (AUDIT score ≥8)	Southampton Traffic Light Test	1,128	393	44.1	58.3%
Moessner[113]	Denmark; screening of subjects attending drug and alcohol outreach centre	Alcohol misusers who were HCV negative	TE	759	175	Not Stated	Not Stated
Harman[157]	United Kingdom; screening of subjects from 2 primary care practices	Hazardous alcohol use, Type 2 Diabetes, raised ALT	TE	920	378 (of whom valid TE in 366 (96.8%)); subgroups of hazardous alcohol misuse (n=174), Type 2 Diabetes (n=211) and raised ALT (n=54)	61.8	67.5%

ALD= Alcoholic liver disease; ALT = alanine aminotransferase; AST = aspartame aminotransferase; APRI = AST:platelet count ratio; AUDIT = Alcohol use disorders identification test; BAAT = score of age≥50 years (1 point), body mass index≥28 kg/m^2 (1 point), ALT≥2 times upper limit of normal, triglycerides≥1.7mmol/L; BARD = weighted score of Body mass index ≥28kg/m^2 (1 point), AST:ALT ratio≥0.8 (2 points), Type 2 Diabetes (1 point); CT = Computer tomography; ELF = Enhanced Liver Fibrosis (combination of hyaluronic acid, TIMP metallopeptidase inhibitor 1 and Procollagen III N-Terminal Propeptide);FIB4 = combination of age, ALT, AST and platelet count; Fibrotest = combination of α2-macroglobulin,age, Apolipoprotein A1, bilirubin, gender, GGT and haptoglobin; HCV = Hepatitis C virus; MRS = Magnetic resonance spectroscopy; NAFLD = Non-alcoholic fatty liver disease; NHANES III = National health and nutrition examination survey; NFS = NAFLD Fibrosis Score (combination of age, hyperglycaemia, body mass index, platelet count, albumin, and AST:ALT ratio); Southampton Traffic Light Test = combination of hyaluronic acid, Procollagen III N-Terminal Propeptide and platelet count; TE = Transient Elastography

Table 2.2: Results of 10 studies reporting liver fibrosis prevalence in unselected subjects of the general population or subjects selected by age alone using a non-invasive test in a community setting

Study (First Author)	Risk Factor Prevalence	Outcome Measure	Non-invasive Test Threshold	Disease Prevalence	Normal ALT (%) (Diseased State)
Baba[147]	BMI≥23 = 33.4% Alcohol consumption >20g/day = 36%	Any liver fibrosis	TE (liver stiffness) ≥5.9kPa	14.4%	55%
Wong[148]	Type 2 Diabetes = 5.2% BMI≥25 = 22.8%	Advanced Liver Fibrosis	TE (liver stiffness) ≥9.6kPa	2%	40%
You[146]	BMI>25 = 41.5% Type 2 Diabetes = 11.9% Hypertension = 25.2%	Significant Liver Fibrosis	TE (liver stiffness) ≥7kPa	6.9%	63.6%
Lemoine[160]	Not Stated	Any Liver Fibrosis	TE (liver stiffness) ≥7.2kPa	11%	Not Stated
Malik[155]	Not Stated	Any Liver Fibrosis	TE (liver stiffness) ≥7kPa	19%	Not Stated
Fabrellas[161]	Hazardous alcohol consumption = 9%	Any Liver Fibrosis	TE (liver stiffness) ≥6.8kPa	5.7%	Not stated
Zelber-Sagi[156]	Type 2 Diabetes = 6.8% Hypertension 37.3% Metabolic syndrome = 18.6%	i) Any Liver Fibrosis ii) Significant Liver Fibrosis iii) Advanced Liver Fibrosis	i) Fibrotest ≥0.22 ii) Fibrotest ≥0.32 iii) Fibrotest ≥0.59	i) 25.7% ii) 12.8% iii) 0.9%	Not Stated
Poynard[154]	Hazardous alcohol = 22.5% BMI≥27 = 32.5% Dysglycaemia = 15.3%	i) Presumed Liver Fibrosis ii) Any Liver Fibrosis	i) Fibrotest>0.48 ii) Fibrotest>0.48 and TE (liver stiffness) ≥7.1kPa	i) 2.8% ii) 0.7%	i) 74.6% ii) 66%
Roulot[112]	Metabolic syndrome = 20.3% BMI≥30 = 17.1% BMI 25-29 = 45.8%	Any liver fibrosis	TE (liver stiffness) ≥8kPa	7.5%	43%
Veysey[149]	NAFLD (fatty liver index>60) = 43.2%	Any Liver Fibrosis	NAFLD Fibrosis Score>0.676	18.9%	Not Stated

ALT = alanine aminotransferase; BMI = Body Mass Index; Fibrotest = combination of α2-macroglobulin,age, Apolipoprotein A1, bilirubin, gender, GGT and haptoglobin; kPa = kilopascals; NAFLD = Non-alcoholic fatty liver disease; NFS = NAFLD Fibrosis Score (combination of age, hyperglycaemia, body mass index, platelet count, albumin, and AST:ALT ratio); TE = Transient Elastography

Table 2.3: Results of 10 studies reporting liver fibrosis prevalence in patients with risk factors for non-alcoholic fatty liver disease (NAFLD) using a non-invasive test in a community setting

Study (First Author)	Risk Factor Prevalence	Outcome Measure	Non-invasive Test Threshold	Disease Prevalence	Normal ALT (%) (Diseased State)
Baba[147]	NAFLD (ultrasound) = 100%	Any liver fibrosis	TE (liver stiffness) ≥5.9kPa	31.0%	Not Stated
Wong[148]	Type 2 Diabetes = 11% Metabolic Syndrome = 47.3%	Advanced Liver Fibrosis	a) TE (liver stiffness) ≥ 9.6kPa b) AST:ALT ≥1.0 c) APRI ≥0.5 d) APRI ≥1.5 e) FIB4 ≥1.30 f) FIB4 ≥ 2.67 g) NAFLD Fibrosis Score ≥0.676 h) BARD ≥2	a) 3.7% b) 12.1% c) 4.5% d) 0% e) 9.8% f) 0.4% g) 0% h) 6.1%	Not Stated
Veysey[149]	NAFLD defined by elevated fatty liver index score	Advanced Liver Fibrosis	NAFLD Fibrosis Score≥0.676	27.9%	Not Stated
Armstrong[56]	Type 2 Diabetes = 38.6% Obesity = 60.3%	Advanced Liver Fibrosis	NAFLD Fibrosis Score ≥0.676	7.6%	N/A (subjects selected due to abnormal LFTs)
Kim[162]	NAFLD (detected on ultrasound) = 100% Type 2 Diabetes = 8.4%	Liver Fibrosis	NAFLD Fibrosis Score ≥0.676	3.2%	Not Stated
Grattagliano[159]	Type 2 Diabetes = 24.3% Metabolic Syndrome = 29.7% BMI≥25 = 89.2%	i) Any Liver Fibrosis (≥F1-F2) ii) Advanced Liver Fibrosis	i) Fibrotest ≥0.32 ii) Fibrotest ≥0.58	i) 53.7% ii) 13.1%	ii) 26.5%

	BMI≥30 = 46.5%				
Williamson[150]	Type 2 Diabetes = 100%	i) Any hepatic fibrosis (whole study population) ii) Any hepatic fibrosis (NAFLD risk only)	i) Hyaluronic acid (HA) >100ng/ml and no joint disease ii) a) HA as above b) BAAT score (≥2) c) BARD Score (2) d) NAFLD fibrosis score ≥0.676	i) 5.7% ii) a) 6.1% ii b) 79.3% ii c) 92.6% ii d) 16.4%	ii) 87.5%
Morling[151]	Type 2 Diabetes = 100%	i) Any Liver Fibrosis (whole study population) ii) Any Liver Fibrosis (NAFLD)	i) and ii) a) APRI≥1.0 b) AST:ALT Ratio≥1.0 c) ELF score ≥ 10.358 d) FIB4 ≥1.30 e) TE (Liver Stiffness) ≥8.7kPa	**Whole study:** i) a) 0.8% i) b) 22.4% i) c) 7.0% i) d) 68.3% i) e) 4.8% **NAFLD subgroup**: ii) a)0.4% ii) b) 16.7% ii) c) 4.3% ii) d) 63.8% ii) e) 4.8%	Not Stated
Das[152]	**Whole population:** BMI≥25 = 7% Abdominal Obesity =11% Dysglycaemia = 13% **NAFLD subgroup:** BMI ≥25 = 25% Abdominal obesity – 39% Dysglycaemia – 26%	Significant Liver Fibrosis	TE (Liver stiffness) ≥8kPa	1.4% of whole population; 15.9% of NAFLD patients; 59% of NAFLD patients with raised ALT	N/A (subjects selected due to raised ALT)

Harman[157]	Type 2 diabetes = 93.4% BMI ≥30 = 49.0% Metabolic syndrome = 49.0%	Significant Liver Fibrosis	TE (liver stiffness) ≥8kPa	33.8%	74.6%

ALT = alanine aminotransferase; AST = aspartate aminotransferase; APRI = AST:platelet count ratio; BAAT = score of age≥50 years (1 point), body mass index≥28 kg/m^2 (1 point), ALT≥2 times upper limit of normal, triglycerides≥1.7mmol/L; BARD = weighted score of Body mass index ≥28 kg/m^2 (1 point), AST:ALT ratio≥0.8 (2 points), Type 2 Diabetes (1 point); BMI = body mass index; ELF = Enhanced Liver Fibrosis (combination of hyaluronic acid, TIMP metallopeptidase inhibitor 1 and Procollagen III N-Terminal Propeptide);FIB4 = combination of age, ALT, AST and platelet count; Fibrotest = combination of α2-macroglobulin,age, Apolipoprotein A1, bilirubin, gender, GGT and haptoglobin; HA = Hyaluronic acid; kPa = kilopascals; NAFLD = Non-alcoholic fatty liver disease; NFS = NAFLD Fibrosis Score (combination of age, hyperglycaemia, body mass index, platelet count, albumin, and AST:ALT ratio); TE = Transient Elastography

Table 2.4: Results of 4 studies reporting liver fibrosis prevalence in patients with hazardous alcohol use using a non-invasive test in a community setting

Study (First Author)	Risk Factor Prevalence	Outcome Measure	Non-invasive Test Threshold	Disease Prevalence	Normal ALT (%) (Diseased State)
Baba[147]	Alcohol consumption >20g/day = 100%	Any liver fibrosis	TE (liver stiffness) ≥5.9kPa	20.5%	Not stated
Sheron[153]	Hazardous alcohol use (Alcohol AUDIT score>15) = 24.4%	Probable Liver Fibrosis	Southampton Traffic Light 'Red' ≥0.921	11%	87.1%
Moessner[113]	Hazardous alcohol use = 60%	Significant Liver Fibrosis	TE (liver stiffness) ≥8kPa	17%	Not Stated
Harman[157]	Hazardous alcohol use = 100% Type 2 diabetes = 11.3% BMI ≥30 = 20.2% Metabolic syndrome = 8.9%	Significant Liver Fibrosis	TE (liver stiffness) ≥8kPa	18.5%	74.1%

ALT = alanine aminotransferase; AUDIT = Alcohol use disorders identification test; BMI = body mass index; kPa = kilopascals; Southampton Traffic Light Test = combination of hyaluronic acid, Procollagen III N-Terminal Propeptide and platelet count; TE = Transient Elastography

Table 2.5: Results of 7 studies reporting liver cirrhosis using a non-invasive test in a community setting

Study (First Author)	Risk Factor Prevalence	Outcome Measure	Non-invasive Test Threshold	Disease Prevalence (% in studied population)	Cirrhosis Aetiology	Normal ALT (%) (Diseased State)
Malik[155]	Not Stated	Cirrhosis	TE – liver stiffness≥7kPa and liver biopsy confirmation	1.7%	Not Stated	Not Stated
Zelber-Sagi[156]	Diabetes = 6.8% Hypertension = 37.3% Metabolic syndrome = 18.6%	Cirrhosis	Fibrotest≥0.75	0.3%	Not Stated	Not Stated
Poynard[154]	Hazardous alcohol 22.5% BMI≥27 – 32.5%	Cirrhosis	Fibrotest>0.48 and TE (liver stiffness) ≥7.1kPa and liver biopsy confirmation	0.1%	NAFLD and ALD (44%), NAFLD (33%), ALD and Hepatitis C (22%)	Not Stated
Roulot[112]	Metabolic syndrome = 20.3% BMI≥30 – 17.1% BMI 25-29 = 45.8%	Cirrhosis	TE – liver stiffness>13kPa	0.76%	Alcohol (56%), Chronic viral hepatitis (44%)	Not Stated
Das[152]	**Whole population**: BMI≥25 = 7% Abdominal Obesity =11% Dysglycaemia = 13% **NAFLD subgroup**:	Cirrhosis	NAFLD (ultrasound, CT, TE –liver stiffness ≥8.0kPa)	0.2% of whole population; 2.4% of those with NAFLD	NAFLD (100%)	Not Stated

	BMI ≥25 = 25% Abdominal obesity – 39% Dysglycaemia – 26%					
Moessner[113]	Not Stated	Cirrhosis	TE – liver stiffness≥12kPa	4%	ALD (100%)	Not Stated
Harman[157]	**Whole population:** Obesity = 34.4% Metabolic syndrome = 31.0% Type 2 Diabetes = 55.8% Hazardous alcohol use = 46.0%	Cirrhosis	TE – liver stiffness >13.0kPa	3.0%	ALD (18.2%) NAFLD (81.8%)	90.9%

ALD= Alcoholic liver disease; ALT = alanine aminotransferase; BMI = Body Mass Index; CT = Computer tomography; Fibrotest = combination of α2-macroglobulin,age, Apolipoprotein A1, bilirubin, gender, GGT and haptoglobin; kPa = kilopascals; NAFLD = Non-alcoholic fatty liver disease; TE = Transient Elastography

Table 2.6: Results of 6 studies reporting liver biopsy findings in patients with an abnormal non-invasive test result

Study (First Author)	Non-invasive Test Threshold	Biopsy performed	Biopsy Results	Disease Aetiology
Lemoine[160]	TE (Liver Stiffness)≥7.2kPa	7/8 (87.5%)	All F0-F1 fibrosis stage (individual staging not stated)	Not Stated
Malik[155]	i) TE (Liver Stiffness) 7-10kPa ii) TE (Liver Stiffness) >10kPa	i) 7/18 (38.9%) ii) 4/4 (100%)	i) No fibrosis 7/7 (100%) ii) F3 Fibrosis 2/4 (50%), Cirrhosis 2/4 (50%)	All patients ALD or NAFLD, but exact percentages not stated
Roulot[112]	i) TE (Liver Stiffness) 8-13kPa ii) TE (Liver Stiffness) >13kPa	i) 18/80 (22.5%) ii) 9/9 (100%)	i) 17/18 (94%) F1 or F2 fibrosis ii) 9/9 (100%) Cirrhosis	i) NAFLD (8), ALD (6), HBV (2), HCV (1), PBC (1) ii) ALD (5), HCV (3), HBV (1)
Grattagliano[159]	Fibrotest ≥0.58	16/34 (47.1%)	F2 Fibrosis 2/16 (12.5%) F3 Fibrosis 14/16 (87.5%),	Not Stated
Moessner[113]	TE (Liver Stiffness)≥12kPa	20/45* (44.4%)	F1 Fibrosis 4/20 (20%) F2 Fibrosis 3/20 (15%) F3 Fibrosis 4/20 (20%) Cirrhosis 9/20 (45%)	Not Stated
Harman[157]	TE (Liver stiffness)≥8kPa	25/98 (25.5%)	Hepatic fibrosis 20/25 (80%) No fibrosis 5/25 (20%)	Not stated

*Biopsy data reported in this study includes both Hepatitis C positive and negative patients. ALD = alcoholic liver disease; Fibrotest = combination of α2-macroglobulin,age, Apolipoprotein A1, bilirubin, gender, GGT and haptoglobin; HBV = Hepatitis B Virus; HCV = Hepatitis C; kPa = kilopascals; NAFLD = Non-alcoholic fatty liver disease; PBC = primary biliary cirrhosis; TE = Transient Elastography

Table 2.7: Studies reporting factors associated with liver fibrosis on logistic regression analysis

Study (First Author)	Outcome Measure	Uni- or Multivariate Analysis	Variable	Odds Ratio (95% CI)	P Value
Baba[147]	Elevated Liver Stiffness (>5.9kPa)	Univariate	BMI 23-25 BMI >25 Alcohol>20g/day Abnormal LFT Fatty Liver APRI	2.52 (1.23-5.01) 3.26 (1.65-6.34) 2.12 (1.23-3.70) 3.88 (2.17-6.94) 5.55 (3.11-9.88) 2.11 (1.06-3.23)	0.012 0.0008 0.0075 <0.0001 <0.0001 0.0001
		Multivariate (BMI and alcohol adjusted)	BMI 23-25 BMI>25	2.21 (1.06-4.46) 3.25 (1.62-6.43)	0.033 0.001
You[146]	Significant Fibrosis	Multivariate (Age, BMI, HOMA-IR, visceral fat area on CT, calcified carotid plaques and carotid IMT adjusted)	BMI ALT Carotid IMT Number of calcified carotid plaques	1.487 (1.009-2.193) 1.078 (1.015-1.145) 3.244 (1.140-9.234) 1.787 (1.055-3.026)	0.045 0.014 0.027 0.031
Zelber-Sagi[156]	Significant Fibrosis (F1-F2 and above)	Multivariate (Age and Sex adjusted; stepwise comparison)	Age Male Gender Obesity Insulin	1.08 (1.04-1.1) 6.74 (2.6-17.4) 2.30 (1.09-4.8) 1.03 (1.001-1.051)	<0.001 <0.001 0.004 0.007
Poynard[154]	Presumed Fibrosis	Multivariate	Age Male Gender Waist Circumference Triglycerides	1.12 (1.10-1.14) 4.31 (2.62-7.08) 1.03 (1.01-1.04) 1.32 (1.21-1.45)	<0.0001 <0.0001 0.0002 <0.0001

			Total Cholesterol Fasting Glucose	0.61 (0.52-0.72) 1.15 (1.05-1.26)	0.04 0.002
	Confirmed Fibrosis	Multivariate	Age Male Gender Waist Circumference Triglycerides	1.13 (1.09-1.16) 6.36 (2.03-22.1) 1.05 (1.02-1.07) 1.22 (1.07-1.39)	<0.0001 0.002 0.001 0.001
Roulot[112]	Elevated Liver Stiffness (>8kPa)	Univariate	Age≥57 years Female Gender Ex-smoker BMI≥30 Elevated Waist Circumference Triglycerides>150mg/dl Diabetes Hypertension GGT≥45IU/L ALT≥40IU/L Platelets<150 10^9/l	2.0 (1.3-3.2) 0.5 (0.3-0.7) 1.7 (1.0-2.8) 3.6 (2.3-5.7) 2.6 (1.7-4.1) 2.0 (1.2-3.2) 3.1 (2.0-4.8) 2.9 (1.7-5.1) 3.4 (2.2-5.4) 6.3 (4.0-10.1) 3.7 (1.2-11.3)	0.003 0.002 0.05 <0.0001 <0.0001 0.004 <0.0001 0.0002 <0.0001 <0.0001 0.03
		Multivariate (factors p<0.20 – above plus alcohol consumption)	Age≥57 years BMI≥30 Elevated Waist Circumference Diabetes GGT≥45IU/L ALT≥40IU/L	1.8 (1.1-3.0) 2.0 (1.0-3.7) 1.9 (1.0-3.5) 1.7 (1.0-2.8) 1.7 (1.0-2.9) 4.2 (2.4-7.2)	0.02 0.04 0.05 0.03 0.04 <0.0001

ALT = alanine aminotransferase; APRI = AST:platelet count ratio; BMI = body mass index; CT= Computer tomography; GGT = gamma-glutamyltransferase; HOMA-IR = Homeostasis model assessment-insulin resistance; IMT = intima-media thickness; kPa = kilopascals

2.6 Discussion

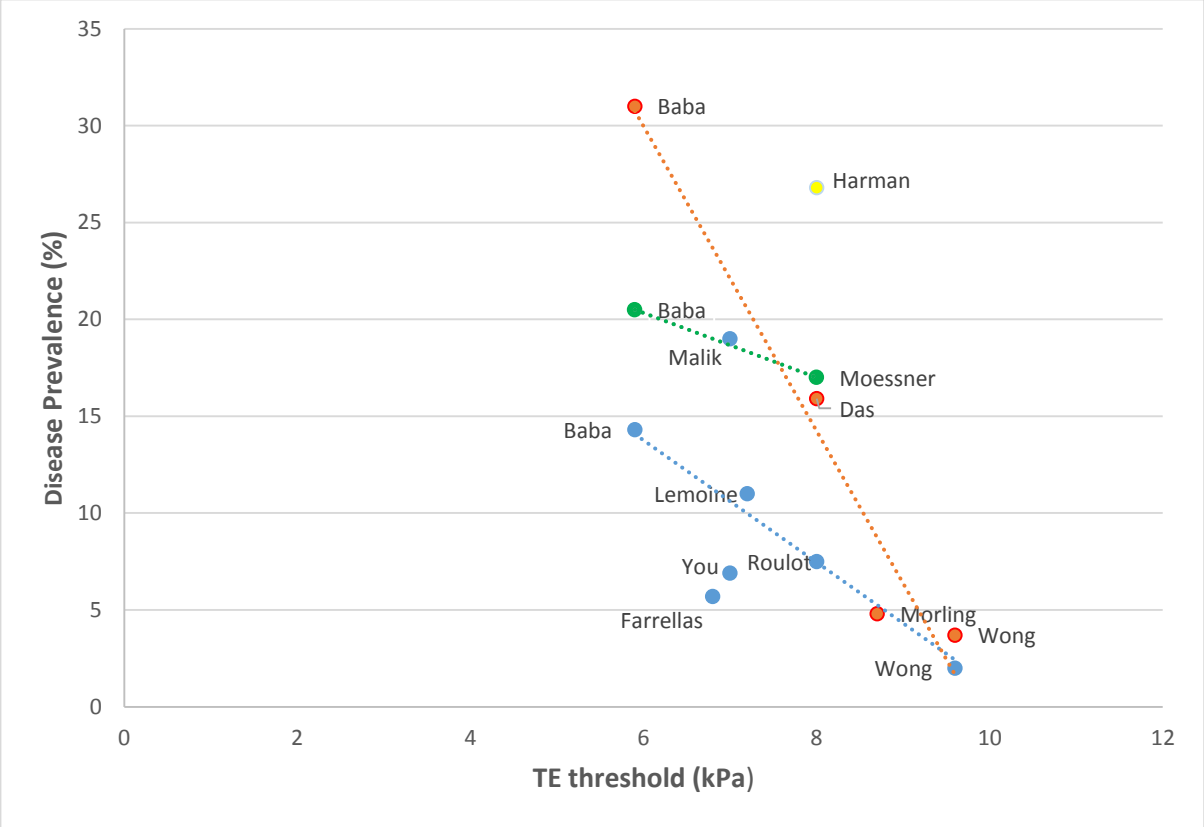
This review has demonstrated that a number of non-invasive tests have the ability to stratify for the severity of liver disease within a community setting. Moreover, when compared to the uptake of other screening programs, the participation of those invited suggests that, as screening tests for use in the community, they are acceptable to patients. The estimates of cirrhosis prevalence (0.1%-1.7%) are greater than previously reported by Fleming *et al* (0.07%)[28] and Jepsen *et al* (0.07-0.13%)[163] which utilised diagnostic codes from patient registries. This increased estimate highlights the burden of undiagnosed chronic liver disease which can be identified in the general population by implementation of case finding strategies and that the true population prevalence is still yet to be firmly established. The presence of a normal ALT in both those with significant liver disease (ranging from 40.0% to 74.6%) and those with cirrhosis (90.9% in one study) is also a clear reminder of the limitations of this test to detect chronic liver disease.

In this review eleven different non-invasive tests were used within heterogeneous population groups. The variation in reported disease prevalence highlights the uncertainty as to which test is most appropriate as demonstrated specifically in the studies by Morling *et al[151]* and Wong *et al[148]* who applied several non-invasive tests to the same cohort of patients resulting in widely differing estimates of prevalence for any liver fibrosis (0.4%-63.8%) and advanced liver fibrosis (0%-12.1%).

Moreover, comparing studies which used the same non-invasive test provided no further clarity as different thresholds were used within different patient populations for the

stratification of liver fibrosis. This is highlighted in Figure 2.2 in which the variation in disease prevalence is demonstrated for all the studies using transient elastography as their non-invasive test

Figure 2.2: Prevalence of liver fibrosis at different transient elastography (TE) thresholds labelled by the first author of each study.



Blue =Studies of the general population

Red = Studies which stratified patients at risk of NAFLD

Green =Studies which stratified patients at risk of ALD

Yellow = Studies which stratified patients at risk of ALD and/or NAFLD.

However, as demonstrated by Roulot *et al [112]* and Moessner *et al [113],* even when similar liver stiffness thresholds for transient elastography were used a wide variation in the histological diagnoses can be observed. An important point to consider is that the pre-test probability of identifying patients with liver fibrosis will vary depending on the patient population being stratified. The studies by Roulot *et al [112]* and Moessner *et al [113]* were completed within the general population compared to patients at risk of ALD and consequently a varied prevalence of disease was observed (7.5% vs 17%, respectively).

The variations in thresholds may be secondary to the use of so called normal populations to determine the upper limit of normal. Roulot *et al*[164] defined a threshold of 8kPa based on the 95th percentile of a healthy non-obese French population without the metabolic syndrome. Conti *et al[165]* evaluated transient elastography in an age restricted (30-60 years) healthy Italian population and reported a threshold of 6.8kPa based on the 95th percentile. Whilst Das *et al* [166] studied a healthy south Asian population without the metabolic syndrome and reported a higher threshold of 8.5kPa based on the 95th percentile. This variation demonstrates that the optimal threshold for defining a specific degree of liver fibrosis is yet to be agreed.

There also appears to be no concordance over which stage of liver fibrosis is clinically important with studies reporting the prevalence of any, significant or advanced liver fibrosis as their outcome measure. In NAFLD, it has been shown that patients with ≥F3 fibrosis have an increased risk of mortality predominantly from cardiovascular and liver related disease [61, 162]. The threshold or strategy may also need to be altered depending on the underlying aetiology. Continued alcohol use has previously been demonstrated to markedly increase the liver stiffness measurement secondary to ongoing steatohepatitis [167]. This

could result in misdiagnosis. However, a period of abstinence has been shown to significantly decrease the liver stiffness measurement which could lead to improved diagnostic accuracy [115]. This may explain the variation in histological findings in the study by Moessner *et al [113]* in which a threshold of ≥12 kPa was used to define cirrhosis but on histology only 45% of patients had evidence of this. Alternatively, this may just be reflective of the tests performance at this threshold. Nguyen-Khac *et al* [140] demonstrated the positive predictive value for cirrhosis in a cohort of 103 patients with hazardous alcohol use as only 68.6% when a higher threshold of 19.5kPa was used. Further research is required to determine whether alternative thresholds are required for patients at risk of alcoholic liver disease or whether a repeat test after a period of abstinence would be a more effective diagnostic strategy.

The use of a liver biopsy as a screening tool is not feasible because of the practicalities of doing an invasive procedure in a community setting, the expense and the low prevalence of disease. Together this results in an unfavourable risk-benefit ratio. Currently all non-invasive tests continue to be validated against histological findings which have their own well documented limitations [98]. From the studies within this review the true diagnostic performance could not be established as a liver biopsy was not completed on all of the patients with an abnormal test result or any patient with a negative test result. Although formal analysis of the quality of included studies was not carried out because they were diagnostic prevalence studies for which a relevant validated quality assessment tool was not found, it should be considered that all included studies are at high risk of methodological bias due to the inherent selection bias for liver biopsy. Completion of longitudinal cohort studies which report hard clinical outcomes of decompensated liver disease and death would enable the true diagnostic performance of a non-invasive test to be assessed along

with identifying and validating the optimum threshold that should be applied. These studies are also imperative given the emerging evidence of the additional prognostic information that these non-invasive markers could provide [127, 162]. Kim *et al* [162] reported that patients with non-alcoholic fatty liver disease who were identified to have advanced fibrosis by non-invasive markers alone (NAFLD fibrosis score (NFS), AST to platelet ratio index (APRI) and Fib-4 score) had a significant increase in mortality, particularly from cardiovascular disease. Boursier *et al [107]* have also recently demonstrated the value of using transient elastography in the context of non-alcoholic fatty liver disease to stratify patients into specific subgroups which correlate with clinical outcomes. Transient elastography was demonstrated to have the best discriminative ability for the prediction of mortality from liver related complications. The clinical outcome studies that have emerged are focused on patients presenting to hospitals with the associated limitations of both referral bias and spectrum bias. Although long term outcomes are awaited from studies of non-invasive tests done specifically in the general population the only feasible option is to use extensively validated tests derived from secondary care. However, it is still not clear whether the thresholds that have been proposed can be used within these populations.

Despite these differences, transient elastography and Fibrotest, were the most frequently used tests being utilised within 3 or more studies, and had their results compared against histological findings. Subsequently these are the most validated non-invasive tests in a general population setting.

Despite liver disease mortality in Europe being comparable to other diseases which are given a higher priority on the public health agenda[20], improved detection of early liver disease in the community continues to make slow progress and is reportedly restricted by available

resources and the considerable numbers of patients at risk[168]. The studies which reported the presence of any liver fibrosis in the general population have demonstrated the potential burden of disease (0.7%-25.7%) although more focussed stratification for advanced liver fibrosis (0.9%-2%) or cirrhosis (0.1%-1.7%) narrowed estimates of prevalence. To date, there has been no recommendation to screen the general population for chronic liver disease due to the concerns about cost and the unknown wider consequences of a false positive or negative result. However, with the increasing incidence of risk factors such as alcohol misuse, obesity and type 2 diabetes, targeting specific high risk populations may initially be more realistic and has recently been recommended by the European Association for the Study of Liver (EASL)[168]. Studies which targeted patients with risk factors of chronic liver disease reported a higher prevalence of advanced liver fibrosis (0%-27.9%) and cirrhosis (2.4%-4%) in comparison to the general population. Health economic evaluations to determine the cost effectiveness of targeting specific patient populations may aid decisions regarding implementation.

Finally, this review demonstrates that the longstanding reliance upon LFTs is misguided and that current strategies are ineffective and missing a large proportion of patients with asymptomatic liver disease; 26.5-87.5% of patients with an abnormal non-invasive test result had an ALT level within the normal range. Strategies which improve risk stratification are urgently required and should not be based upon abnormalities within LFTs alone. Targeting patients with known risk factors will improve the diagnostic yield and be more effective in identifying patients with asymptomatic chronic liver disease. Furthermore, employing a risk stratification algorithm which also incorporates simple patient related risk factors such as those identified through the multivariate analysis (raised BMI, elevated waist circumference, age and gender) could increase the likelihood of identifying patients with liver fibrosis.

In conclusion, this systematic review has demonstrated an appreciable burden of undetected chronic liver disease within the community setting in a diverse set of populations. However, an optimal strategy for risk stratification is not yet clear. Targeting specific populations at risk of chronic liver disease may initially be more realistic than screening the general population. Indeed as demonstrated in this review, studies which have highly selected the population have reported a higher prevalence of disease compared to targeting the general population. However, there still remain a number of unanswered questions about implementing a targeted risk stratification pathway including the optimal method of diagnosing chronic liver disease in the community and which at risk populations should be targeted. The significance of specific risk factors (e.g. obesity) on the risk of clinically significant liver disease within a community population is still unknown. Utilising transient elastography, which as demonstrated from this review is one of only two non-invasive tests that have been validated in a community setting thus far, we report the results of implementing our own risk stratification pathway in Chapter 3 with the specific aim of elucidating the significance of a raised body mass index as a risk factor on its own or in combination with other risk factors for chronic liver disease.

3 Obesity as a risk factor for chronic liver disease. How important is it? Risk stratification using transient elastography in a community setting.

3.1 Chapter summary

This chapter follows on from previous work carried out by our research group in which implementation of a community based risk stratification pathway, which used transient elastography as a risk stratification tool, and targeted patients with hazardous alcohol use and/or type 2 diabetes, was demonstrated to be feasible and successful. In this study we replicated the pathway and aimed to elucidate the significance of a raised body mass index on its own or in combination with other risk factors for chronic liver disease. Seven hundred and three patients attended the pathway of which 82 (11.7%) had an elevated transient elastography reading. An elevated transient elastography reading was approximately as common in patients with just a raised body mass index (≥27.5kg/m^2) (8%) as it was in patients with more recognised solitary risk factors (Type 2 diabetes, 10%; Hazardous alcohol use 3.5%). A raised body mass index in combination with other risk factors further increased the proportion of patients with an elevated transient elastography reading. Obesity as a single or combined risk factor for chronic liver disease is significant.

3.2 Introduction

3.2.1 Transient elastography as a risk stratification tool

As demonstrated in chapter 2 of this thesis, transient elastography is one of only two non-invasive tests which have been validated in a community setting to stratify for the severity of liver disease. A reading is obtained during a 10 minute examination using an ultrasound transducer probe and as a point of care diagnostic test the result can be given and explained to the patient during the same consultation.

Use of transient elastography as a risk stratification tool in the community is appealing secondary to it ease of use, reproducibility, diagnostic accuracy, provision of timely results and the fact that it is non-invasive. Consequently, recent studies have focused on its use within this context as demonstrated in the systematic review in chapter 2. Roulot *et al* [112] screened 1358 subjects who were >45 years old from a general population who attended for a medical check up. Eighty nine (7.5%) asymptomatic patients were identified to have an elevated transient elastography reading consistent with significant liver fibrosis. A liver biopsy subsequently confirmed a diagnosis of cirrhosis in all 9 patients who had a liver stiffness measurement >13kPa. In the 18 patients who agreed to a biopsy with a reading between 8-13kPa, all except one had evidence of liver fibrosis. Of note, 43% of the patients with an elevated transient elastography reading had normal liver function tests and may not otherwise have been identified. Moessner *et al* [113] demonstrated the successful use of transient elastography as a screening tool in a different cohort of patients by targeting drug users attending treatment centres. Seventeen percent of the patients screened had an elevated reading consistent with significant liver fibrosis.

3.2.2 Previous work by our research group

Our own research group has previously conducted a cross sectional study to evaluate the feasibility and success of implementing an alternative diagnostic algorithm for chronic liver disease in a primary care setting which included transient elastography as a risk stratification tool [157]. Patients identified to have a lifestyle related risk factor for chronic liver disease (hazardous alcohol use +/- type 2 diabetes) or who had a persistently raised ALT level with no other risk factor and a negative non-invasive liver screen were invited to attend the pathway based within their own GP practice (See Appendix 7.2 for pathway).

Patients initially had an indirect serum marker completed which had a high negative predictive value to screen out those with a low probability of having liver fibrosis. Patients with hazardous alcohol use as their risk factor were stratified using the AST:ALT ratio whilst the BARD score (weighted score of body mass index ≥28 kg/m^2 (1 point), AST:ALT ratio≥0.8 (2 points), Type 2 Diabetes (1 point)) was used for patients with type 2 diabetes or a persistently raised ALT. Patients with a result above the defined threshold were invited back to have a transient elastography reading at their practice.

Nine hundred and twenty patients were identified to have a risk factor with 504 patients accepting the invitation to attend the pathway. A normal indirect serum marker was recorded in 62 (12.3%) patients and thus this subgroup underwent no further investigations. Subsequently, 378 patients had a transient elastography reading completed in which 98 patients (26.8% of valid scans) were identified to have an elevated liver stiffness measurement consistent with clinically significant liver disease. Importantly, 72.4% of patients with an elevated reading had normal liver function tests and would not have been

identified by the diagnostic pathway used within clinical practice at the time of the study. However, obesity as a solitary risk factor was not studied thus the proportion of disease within this at risk group and its significance as a solitary or dual risk factor for chronic liver disease remains unclear.

3.2.3 Obesity as a risk factor for chronic liver disease

As described in the introduction of this thesis, cirrhosis is now responsible for 2% of all deaths worldwide with mortality rates continuing to increase in some western countries including the United Kingdom (UK) [18, 27]. Excessive alcohol consumption has long been acknowledged as the predominant risk factor. However, with the increasing prevalence of type 2 diabetes, and obesity in particular, within the general population, non-alcoholic fatty liver disease (NAFLD), the hepatic manifestation of the metabolic syndrome, is now estimated to affect 25% of the global population [55].

Obesity or a raised body mass index (BMI (kg/m^2)) has been independently associated with liver fibrosis or a surrogate measure of clinically significant liver disease (e.g. elevated liver stiffness using transient elastography) [112, 126, 169]. The risk of advanced liver fibrosis correlates with additional components of the metabolic syndrome including an elevated waist circumference as a surrogate measure of abdominal obesity [170]. This correlation is observed even in the absence of type 2 diabetes as a feature of the metabolic syndrome [171]. Similarly, in patients with hazardous alcohol use and a raised BMI a synergistic effect on liver disease mortality has also been observed [172, 173].

Obesity is a major global health challenge and has been described as a pandemic of the 21st century. Despite these warnings there has been no successful demonstration of reversing

this trend with public health measures [100]. As a consequence, this metabolic risk factor has had a dramatic impact on the increasing incidence and prevalence of multiple co-morbidities including chronic liver disease in which the underlying risk factor profile is now changing.

In view of the increasing morbidity and mortality associated with liver disease and the unrelenting rise in underlying risk factors, case finding strategies have been recommended to actively identify patients [168]. The findings from the systematic review reported in chapter 1 demonstrated the feasibility and success of a risk factor based approach in a community based setting [174]. Indeed implementation of our own risk stratification pathway as described above demonstrated a 140% increase in the diagnosed cases of cirrhosis within the studied community population [157]. Further analysis demonstrated that the presence of cirrhosis was significantly increased in obese patients with the predefined risk factors of type 2 diabetes or hazardous alcohol use [175].

3.2.4 Aims

The aim of this study was to characterise the risk of clinically significant liver disease, assessed by transient elastography within subpopulations of a community who were stratified based on their risk factors of a raised BMI (≥27.5kg/m^2) and/or type 2 diabetes and/ or hazardous alcohol use. The significance of a BMI ≥27.5kg/m^2 as a single or combined risk factor for chronic liver disease would be analysed.

3.3 Methods

3.3.1 Study approvals

Local regulatory approval was obtained from the Leicester Research Ethics Committee (13/EM/0123) and written informed consent was gained from patients. The study was performed according to the Good Clinical Practice (GCP) principals and sponsored by the University of Nottingham.

3.3.2 Study setting

This is a prospective study with recruitment from a primary care practice in inner city Leicester, England. Based on the number of patients at risk (10%) within the community population in the previous study by Harman *et al* [157] and the number of additional patients who would be identified due to the added risk factor of a raised BMI (approximately 25% of the adult primary care population), primary care practices with a smaller sized adult population (approximately 5000 adults) were approached to try and ensure all the patients at risk could be invited to the pathway and risk stratified within the time frame of the study. The primary care practice which agreed to implement the risk stratification pathway had a total adult population of 4150 adults. The study ran from January 2015 until March 2016. Clinical, anthropometric and biochemical data was obtained from the electronic primary care records (SystmOne, TPP, UK) within which data is stored as searchable numerical values or prospectively coded 'Read codes' (See Appendix 7.3 for examples). These Read codes, are a coded thesaurus of clinical terms that provide a standardised format for general practitioners to record patient findings and procedures, they have been used in the National Health Service (NHS) since 1985 and are part of standard clinical care.

3.3.3 Patient selection

Recruitment occurred via an invitation to attend a community based risk stratification pathway for chronic liver disease (outlined below). Patients were initially identified from the electronic primary care records. Adults (≥ 18 years) with one or more lifestyle related risk factors for chronic liver disease at the start of the study were invited. These included:

1. Hazardous alcohol use – defined as >14 units/week for women and >21 units/week for men, or an AUDIT questionnaire score ≥ 8, or presence of a Read code for alcohol misuse.

2. Type 2 diabetes - presence of a Read code related to the diagnosis

3. BMI ≥27.5 kg/m^2 – presence of a numerical value recorded within the past 5 years. A lower BMI cut off for obesity (≥27.5 kg/m^2) was agreed a priori for all patients included within the study due to the increased prevalence of people with Asian ethnicity in this population. This is in accordance with the World Health Organisation [176] who recommend different cut off points for the Asian population due to their higher risk of type 2 diabetes and cardiovascular disease at a lower BMI compared to European populations. A lower cut off ensured that patients of Asian ethnicity whose BMI was lower than the international cut off for obesity (30.0 kg/m^2) but who were still at high risk of chronic liver disease would be invited to attend the risk stratification pathway.

Patients with any of the following were ineligible and not invited to attend the risk stratification pathway: 1. Contraindication to undertaking a transient elastography reading (e.g. pregnancy, implantable cardiac device) 2. Known diagnosis of chronic liver disease 3.

Known malignancy or other terminal illness 4. Inability to consent to investigation or housebound and therefore unable to attend the practice.

3.3.4 Transient elastography

Transient elastography is a non-invasive diagnostic test which has been described in the introduction of this thesis (section 1.5.1).

To obtain a reading the patient was placed in the dorsal decubitus position with the right hand behind their head and the tip of the ultrasound transducer probe placed within an intercostal space overlying the right lobe of the liver. The M probe was used initially in all patients with the XL probe used if a valid reading could not be obtained. Ten valid measurements were collected with either the M or the XL probe with the median value reported as the liver stiffness measurement. Examinations unable to record any valid readings were deemed failures. As an indicator of variability the ratio of the interquartile range of the liver stiffness to the median value (IQR/M) were also recorded. Examinations with fewer than 10 measurements and an IQR/M >30% were considered potentially unreliable according to the manufacturer's recommendations at the time of the study. Three experienced operators performed all the TE examinations as per the manufacturer's recommendations. All operators had completed more than 100 examinations prior to the start of the study using the portable Fibroscan FS402 device (Echosens™, Paris).

A threshold of ≥8.0kPa was agreed a priori to define elevated liver stiffness consistent with clinically significant liver disease irrespective of which probe (M or XL) was used to obtain a reading. This threshold has been used within other community based screening programmes

[112] and has been demonstrated to have a high negative predictive value for advanced fibrosis [139].

3.3.5 Enhanced liver fibrosis (ELF) scores

A subset of patients who attended the pathway also consented for an extra blood sample to be taken so the enhanced liver fibrosis score (ELF) could be calculated. Details of this direct serum marker have been described in the introduction of this thesis (section 1.5.2).

Blood samples were collected into plain blood collection tubes and allowed to coagulate at an ambient temperature (18-22°c). The samples were then centrifuged at 2000g for 10 minutes before 500µl was aliquoted into an appropriately labelled cryovial. Aliquots were immediately frozen on liquid nitrogen and stored in logged storage boxes at -80°c.

The serum samples were subsequently analysed for levels of tissue inhibitor matrix metalloproteinase 1 (TIMP1), hyaluronic acid (HA) and terminal peptide of procollagen III (PIIINP) at an independent reference laboratory (iQur Limited, London, UK). The ELF score is calculated using an established algorithm as per the manufacturer's instructions detailed below:

$$\text{ELF score} = 2.494 + 0.846 \ln(C_{HA}) + 0.735 \ln(C_{PIIINP}) + 0.391 \ln(C_{TIMP1})$$

A cut off of ≥9.8 was used to define clinically significant liver disease in accordance with the manufacturer's recommendation [177, 178] and comparable to the cut off used in this study for transient elastography.

3.3.6 Risk stratification pathway

The risk stratification pathway previously used by the research group was amended for use in this study [157]. Along with including the additional risk factor of a raised BMI (≥27.5kg/m^2) it was no longer a requirement for the patient to have an indirect serum marker prior to having a transient elastography reading. The inclusion of this step did not screen out a large number of patients in the feasibility study (12.3%) and, as demonstrated in chapter 2, pathways with multiple steps were shown to have a decline in uptake [153].

Therefore to make the pathway simpler, once a patient was identified as having a lifestyle related risk factor for chronic liver disease (raised BMI (≥27.5kg/m^2) and/or type 2 diabetes and/ or hazardous alcohol use), they were invited to attend directly for a transient elastography reading based within their own primary care practice (See Appendix 7.4 for pathway). Following the scan all patients were given lifestyle advice irrespective of their result. All patients with an elevated transient elastography reading (TE ≥8.0kPa) were invited back to see a hepatologist within the community where further investigations were organised if deemed appropriate. Following the transient elastography reading and any further investigations a clinical diagnosis was made.

3.3.7 Statistical methods

Statistical analysis was completed using Stata version 14.2 (StataCorp LP). Characteristics of the study cohort are presented as numbers (percentage) for categorical data, and medians (IQR) for non-normally distributed continuous data. The Shapiro-Wilk test was used to test the normality of the data. Variables were compared between all the adult patients in the primary care practice and the study cohort and between the study patients who had been stratified by their transient elastography reading. We used chi squared tests for comparisons between categorical data and the Wilcoxon signed rank test for non-normally distributed

continuous data. We constructed univariate and multivariate logistic regression models of the associations of an elevated transient elastography reading (≥8.0 kPa), considering associations with and between BMI, age, gender, type 2 diabetes, hazardous alcohol use, being a previous smoker, hypertension, hyperlipidaemia and ischaemic heart disease. A sub group analysis was completed on those patients who only had a raised BMI (≥27.5 kg/m^2) as a solitary risk factor for chronic liver disease. The likelihood ratio test was used to test the goodness of fit between models.

In order to further evaluate a raised BMI as a single or combined risk factor we report the odds ratio and 95% confidence intervals for an elevated TE reading (≥8.0 kPa) across BMI categories within three different subgroups of the study cohort (raised BMI only, type 2 diabetes and a raised BMI, hazardous alcohol use and a raised BMI). Finally we report the odds ratios for an elevated TE reading (≥8.0 kPa) across a range of BMI categories in the subset of patients studied who had type 2 diabetes or hazardous alcohol use as a risk factor. This analysis was repeated in a subgroup of patients who had an ELF score to determine if the same trend was observed across BMI categories using a different non-invasive test for liver fibrosis. We report the odds ratio and 95% confidence intervals for an elevated ELF (≥9.8) score across BMI categories within the same subgroups listed above. Lastly, to determine whether the transient elastography readings could be falsely elevated due to a patient's BMI, the possibility of interaction between ELF and BMI in their relationship with transient elastography was tested via a likelihood ratio test between models with and without a multiplicative interaction term in the subgroup of patients who had both an ELF score and a transient elastography reading. In these models a binary exposure for BMI was created by stratifying patients based on whether they were obese (BMI ≥30 kg/m^2) or not.

3.4 Results

3.4.1 Baseline characteristics of the cohort

The primary care practice had a total adult population of 4150 of which 1150 patients (27.7%) were identified to have at least one of the defined risk factors for chronic liver disease and eligible to be invited to attend the community risk stratification pathway (Table 3.1). Of these, 703 patients attended the pathway of which 538 had a BMI ≥27.5 kg/m^2 as a risk factor, 171 were diagnosed with type 2 diabetes and 165 had been identified to have hazardous alcohol use. The characteristics of the study patients are outlined in Table 3.1. The median age of the cohort was 59 (IQR 48-69) and 51.8% were male. The majority of the patients were white (70.0%) although this was lower than the general population (87.2% in the UK) due to the high percentage of patients with Asian ethnicity (22.9%) in the community in which the risk stratification pathway was implemented. However, the proportion of patients with varying ethnicities who attended the pathway was similar in comparison to the census data [179] of the local area (Table 3.2). Seventy seven percent of the cohort had a single risk factor, whilst 21.3% had a combination of two and 1.4% had all three risk factors. The median BMI was 29.5 (IQR 27.6-32.9); 46.2% of the patients were obese with a BMI ≥30.0 kg/m^2.

3.4.2 Risk stratification of all patients

Of the 703 patients who attended the pathway, 82 had a transient elastography reading of ≥8.0 kPa consistent with clinically significant liver disease. The characteristics of these patients are outlined in Table 3.3 stratified by their TE reading. Patients with an elevated reading were significantly older, had a raised BMI and had been diagnosed with other features of the metabolic syndrome (hypertension and hyperlipidaemia). In the subset of patients (n=656) in which the ALT was available there was also a significant difference in the

average (median) between the two groups as well as the proportion with a raised ALT (≥45 U/L). However, only 25.9% of patients with an elevated TE reading also had an ALT level above the upper limit of normal.

Table 3.1*:* Baseline characteristics of all adult patients in the practice compared to study patients undergoing transient elastography

Characteristic	Study patients (n=703)	All adult patients (n=4150)	p value
Gender – Male n (%)	364 (51.8%)	2110 (50.8%)	0.647
Age n (%)			
18-30	28 (4.0%)	860 (20.7%)	<0.001
31-40	58 (8.3%)	791 (19.1%)	
41-50	121 (17.2%)	768 (18.5%)	
51-60	183 (26.0%)	677 (16.3%)	
61-70	168 (23.9%)	494 (11.9%)	
71-80	115 (16.4%)	326 (7.9%)	
>80	30 (4.3%)	234 (5.6%)	
BMI kg/m^2			
<25	93 (13.2%)	1686 (40.6%)	<0.001
25-29.9	282 (40.1%)	1226 (29.5%)	
>30	325 (46.2%)	727 (17.5%)	
missing	3 (0.4%)	511 (12.3%)	
Risk factor n (%)*			
Hazardous alcohol use	165 (23.5%)	334 (8.0%)	<0.001
Type 2 diabetes	171 (24.3%)	298 (7.2%)	<0.001
BMI ≥27.5 kg/m^2	538 (76.5%)	1081 (26.0%)	<0.001
Metabolic risk factors n (%)			
Hypertension	287 (40.8%)	826 (19.9%)	<0.001
Hyperlipidaemia	296 (42.1%)	338 (8.1%)	<0.001
Ischaemic heart disease n (%)	58 (8.3%)	238 (5.7%)	0.010

*Patients may have multiple risk factors and therefore the total number of patients will be more than the total number of adult patients in the study/ GP practice.

BMI = Body Mass Index

Table 3.2: Ethnicity of patients within the study cohort and the local area

Ethnicity	Census data (n/%)	Study (n/%)
White	10848 (64.6%)	492 (70.0%)
Asian	4427 (26.3%)	161 (22.9%)
Black	420 (2.5%)	24 (3.4%)
Other	541 (3.2%)	26 (3.7%)
Mixed	569 (3.4%)	-
Total	16805 (100%)	703 (100%)

Table 3.3: Baseline characteristics of all study patients stratified by their transient elastography reading (n=703)

Characteristic	TE		p value
	<8.0 kPa (n=621)	≥8.0 kPa (n=82)	
Gender – Male n (%)	317 (51.1%)	47 (57.3%)	0.286
Age*	58 (14.3)	62 (12.6)	0.012
Ethnicity n (%) White Asian Black/ Other	 438 (70.5%) 142 (22.9%) 41 (6.6%)	 54 (65.9%) 19 (23.2%) 9 (11.0%)	0.337
Metabolic risk factors n (%) Hypertension Hyperlipidaemia	 235 (37.8%) 248 (40.0%)	 52 (63.4%) 48 (58.5%)	 <0.001 0.001
BMI kg/m^2 <25 25-29.9 30-34.9 ≥35.0	 88 (14.2%) 268 (43.4%) 181 (30.0%) 81 (13.1%)	 5 (6.1%) 14 (17.1%) 29 (35.4%) 34 (41.5%)	<0.001
Ischaemic heart disease n (%)	48 (7.7%)	10 (12.2%)	0.161
ALT U/L** (n=656)	24 (18-33)	32 (24-45)	<0.001
ALT ≥45 U/L (n=656)	60 (10.4%)	21 (25.9%)	<0.001
Platelets 10^9/L** (n=637)	246.5 (207-291)	235 (199-296)	0.627

*mean (SD) ** Median (IQR)

ALT = Alanine aminotransferase; BMI = Body mass index; kPa = kilopascal; TE = transient elastography

Of the patients who had a raised BMI (≥27.5 kg/m^2) as a single risk factor for chronic liver disease, 8% had a TE reading ≥8.0 kPa. This proportion was similar to the patients who only had type 2 diabetes as a risk factor (10%). In those patients with hazardous alcohol use as a single risk factor the proportion with a TE reading ≥8.0 kPa was lower (3.5%) although this was not significantly different from the proportions observed with the other solitary risk factors (Table 3.4).

Table 3.4: Proportion of patients with an elevated transient elastography reading according to the underlying risk factor(s).

Risk factor n (%)		**TE <8kPa**	**TE ≥8.0 kPa**	**95% CI**
Single	BMI >27.5 kg/m^2	356 (92.0%)	31 (8.0%)	5.5-11.2%
	Type 2 diabetes	63 (90.0%)	7 (10.0%)	4.1-19.5%
	Hazardous alcohol use	82 (96.5%)	3 (3.5%)	0.7-9.9%
Dual	Type 2 diabetes + BMI >27.5 kg/m^2	54 (66.7%)	27 (33.3%)	23.2-44.7%
	Hazardous alcohol use + Type 2 diabetes	10 (100%)	0 (0%)	0-30.8%
	Hazardous alcohol use + BMI >27.5 kg/m^2	49 (83.0%)	10 (17.0%)	8.4-29.0%
All 3 risk factors	Type 2 diabetes + BMI >27.5 kg/m^2 + Hazardous alcohol use	6 (60.0%)	4 (40.0%)	12.2-73.8%

p value = <0.001

*Chi squared test between the solitary risk factors and the proportion of patients with normal and elevated TE readings:

Hazardous alcohol use vs BMI >27.5 kg/m^2 p=0.15

Hazardous alcohol use vs Type 2 diabetes p=0.10

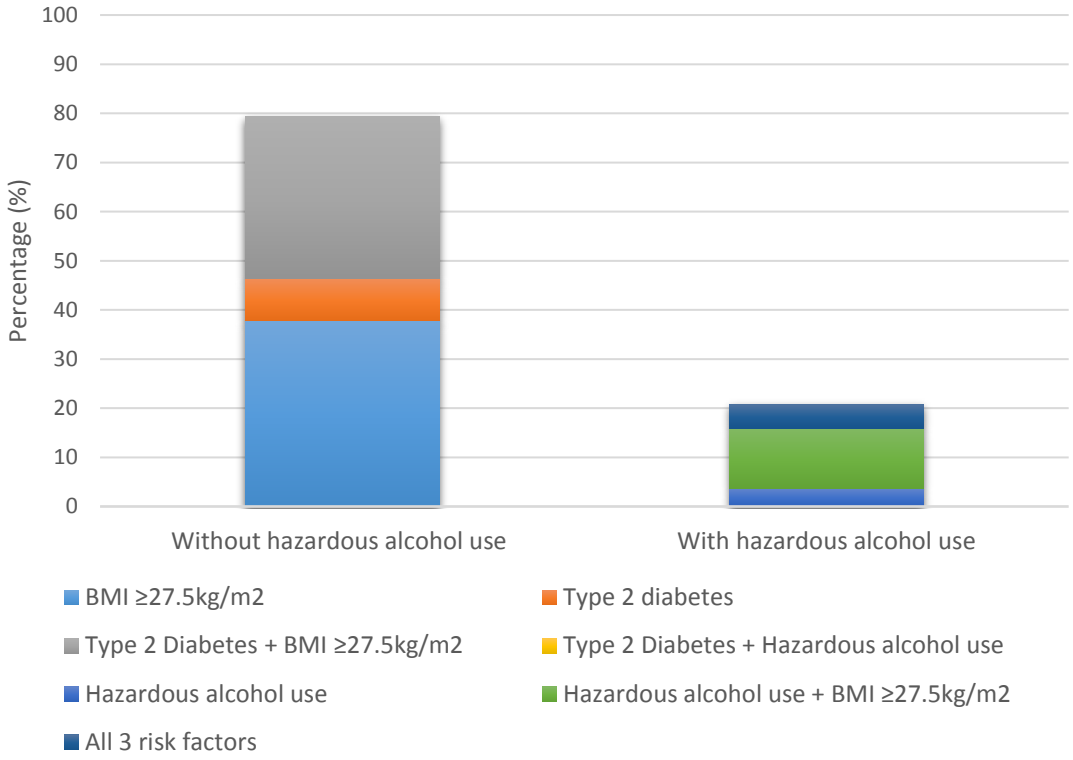
Type 2 diabetes vs BMI >27.5 kg/m^2 p=0.58

BMI = Body mass index; kPa = kilopascal; TE = Transient elastography

The proportion of patients with a TE reading ≥8.0 kPa increased with additional risk factors. Seventeen percent of patients with hazardous alcohol use and a raised BMI had a TE reading

≥8.0 kPa. An even higher proportion was observed in patients who had type 2 diabetes and a raised BMI (33%) and in those with all three risk factors (40%) (Table 3.4). The majority of patients (79.3%) with a TE reading ≥8.0 kPa did not have hazardous alcohol use as an underlying risk factor (Figure 3.1).

Figure 3.1: Percentage of patients with an elevated TE reading (≥8.0 kPa) (n=82) according to whether the underlying risk factor included hazardous alcohol use or not.



BMI = Body mass index; kPa = kilopascal; TE = Transient elastography

A univariate logistic regression analysis identified an increasing BMI and age, a history of smoking and a diagnosis of type 2 diabetes, hypertension and hyperlipidaemia as significant

variables associated with a TE reading ≥8.0 kPa. Using the dichotomised variables of BMI as a risk factor (≥27.5 kg/m^2) or obesity (≥30 kg/m^2) in the univariate analysis instead of BMI as a continuous variable resulted in a significant odds ratios of 2.39 and 4.27 respectively. This is comparable to the odds ratio of having type 2 diabetes as a risk factor for chronic liver disease (odds ratio = 3.17). In the multivariate analysis only increasing BMI and age, male gender and having a diagnosis of type 2 diabetes remained significant variables. For every 1kg/m^2 increase in BMI the odds of having an elevated TE reading (≥8.0 kPa) increased by 19% (Table 3.5).

Table 3.5: Univariate and multivariate logistic regression analysis of the variables associated with an elevated TE reading (≥8.0 kPa) in all patients (n=703)

	Univariate analysis		**Multivariate analysis***	
Variable	**Odds ratio (95% CI)**	**P value**	**Odds ratio (95% CI)**	**P value**
BMI	1.15 (1.10-1.20)	<0.001	1.19 (1.14-1.25)	<0.001
Age	1.02 (1.00 – 1.04)	0.013	1.02 (1.002-1.04)	0.032
Gender	1.29 (0.81-2.05)	0.285	1.81 (1.06-3.10)	0.031
Type 2 diabetes as a risk factor for CLD	3.17 (1.97-5.09)	<0.001	3.11 (1.76-5.50)	<0.001
Hazardous alcohol use as a risk factor for CLD	0.84 (0.48-1.47)	0.528		
Dx of Hypertension	2.85 (1.77-4.59)	<0.001		
Dx of Hyperlipidaemia	2.12 (1.33-3.39)	0.002		
Dx of Ischaemic heart disease	0.81 (0.54-1.22)	0.338		

Previous smoker	1.65 (1.02-2.66)	0.043		

*Adjusted for age/gender/ ethnicity

BMI = Body mass index; CLD = Chronic liver disease; Dx = diagnosis; kPa = kilopascal; TE = Transient elastography

3.4.2.1 BMI ≥27.5 kg/m^2: A single risk factor

Of the 703 people who attended the pathway, 387 had a raised BMI (≥27.5 kg/m^2) as their only risk factor. (The characteristics of these patients are outlined in Table 3.6 stratified by their TE reading.) Patients with an elevated reading were significantly more likely to have a higher BMI and have a diagnosis of hypertension. The odds of a TE reading ≥8.0 kPa significantly increased with increasing BMI. In comparison to those patients who had a BMI between 27.5-29.9 kg/m^2 the odds of having a TE ≥8.0 kPa increased threefold (OR = 3.61, 95% CI 1.13-36.52, p value = 0.03) for those with a BMI between 30-34.9 kg/m^2 whilst having a BMI≥35 kg/m^2 increased the odds ratio to 11.31 (95% CI 3.51-36.52; p value <0.001). This trend was also observed in those patients with dual risk factors (Figure 3.2).

Table 3.6: Baseline characteristics of patients undergoing transient elastography with a raised BMI (≥27.5kg/m^2) as their only risk factor (n=387)

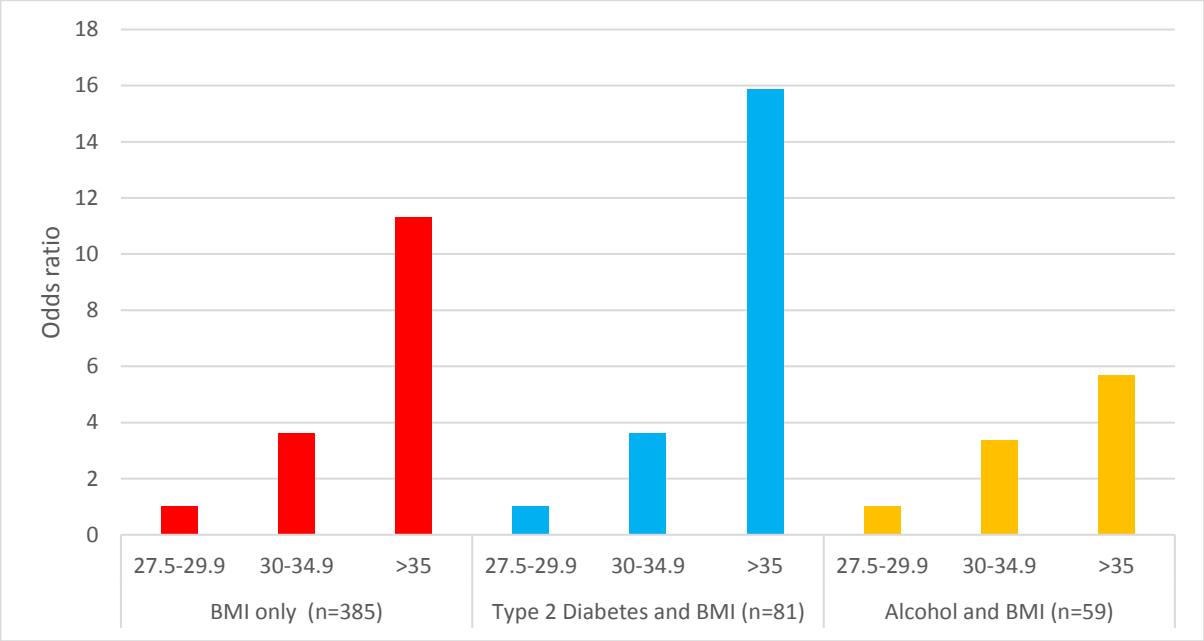
Characteristic	LSM		p value
	<8.0 kPa (n=356)	**≥8.0 kPa (n=31)**	
Gender – Male n (%)	153 (43.0%)	14 (45.2%)	0.814
Age*	55.1 (15.0)	58.3 (12.3)	0.252
Ethnicity n (%)			
White	259 (72.8%)	22 (71.0%)	0.548
Asian	70 (19.7%)	5 (16.1%)	
Black/ Other	27 (7.6%)	4 (12.9%)	
Metabolic risk factors n (%)			
Hypertension	100 (28.1%)	16 (51.6)	0.006
Hyperlipidaemia	107 (30.1%)	12 (38.7%)	0.317
BMI kg/m^2			
27.5-29.9	154 (43.5%)	4(12.9%)	<0.001
30-34.9	137 (38.7%)	12 (38.7%)	
≥35.0	63 (17.8%)	15 (48.4%)	
Ischaemic heart disease n (%)	24 (6.7%)	3 (9.7%)	0.538
ALT U/L (n=350)**	24 (19-33.5)	33.5 (21-59)	0.001
ALT ≥45 U/L (n=350)	33 (10.3%)	10 (33.3%)	<0.001
Platelets 10^9/L (n=347)**	246 (206-287)	261 (210-305)	0.345

*mean (SD)

** median (IQR)

ALT = Alanine aminotransferase; BMI = Body mass index; kPa = kilopascals; LSM = liver stiffness measurement; TE = transient elastography

Figure 3.2: A comparison of odds ratios for TE≥8.0 kPa across different BMI categories according to a raised BMI (≥27.5 kg/m^2) as a single or dual risk factor



	Raised BMI (n=385)			Type 2 Diabetes and Raised BMI (n=81)			Hazardous Alcohol use and Raised BMI (n=59)		
BMI category (kg/m^2)	**27.5-29.9**	**30-34.9**	**≥35**	**27.5-29.9**	**30-34.9**	**≥35**	**27.5-29.9**	**30-34.9**	**≥35**
Odds Ratio*	1	3.61	11.32	1	3.62	15.87	1	3.35	5.68
95% CI		1.13-11.52	3.51-36.52		0.79-16.57	3.19-78.94		0.56-20.04	0.70-45.82
p value		0.03	<0.001		0.097	0.001		0.185	0.103

*Adjusted for age/ gender/ ethnicity

BMI = Body mass index; kPa = kilopascal; TE = Transient elastography

In those patients (n=350) in which the ALT was available a significant difference between the two groups was observed, but only a third of those with a TE reading ≥8.0 kPa also had an ALT level above the upper limit of normal. A univariate logistic regression analysis identified

an increasing BMI and a diagnosis of hypertension as significant variables associated with a TE ≥8.0 kPa. In the multivariate analysis only an increasing BMI remained a significant association (Table 3.7). Of the 31 patients with a TE ≥8.0 kPa, 51.6% had a diagnosis of hypertension and 38.7% had a diagnosis of hyperlipidaemia. In 48.4% of patients a raised BMI (≥27.5 kg/m^2) was their only diagnosed metabolic risk factor (Table 3.8)

Table 3.7: Univariate and multivariate logistic regression analysis of the variables associated with an elevated TE reading (≥8.0 kPa) in patients with a raised BMI (≥27.5 kg/m^2) as a single risk factor (n=387)

	Univariate analysis		**Multivariate analysis***	
Variable	**Odds ratio (95% CI)**	**P value**	**Odds ratio (95% CI)**	**P value**
BMI	1.17 (1.10-1.25)	<0.001	1.20 (1.12-1.29)	<0.001
Age	1.01 (0.99-1.04)	0.253		
Gender	1.09 (0.52-2.29)	0.814		
Dx of Hypertension	2.73 (1.30-5.73)	0.008		
Dx of Hypercholesterolaemia	1.47 (0.69-3.13)	0.319		
Dx of Ischaemic heart disease	0.67 (0.19-2.38)	0.541		
Previous smoker	1.60 (0.74-3.46)	0.236		

BMI = Body mass index; Dx = diagnosis; kPa = kilopascal; TE = Transient elastography

Table 3.8: Metabolic risk factors in patients with a raised BMI (≥27.5 kg/m^2) as a single risk factor and an elevated TE reading (≥8.0 kPa)

BMI (kg/m^2)	TE ≥8.0 kPa	Hypertension	Hyperlipidaemia	Raised BMI (≥27.5kg/m^2) as only metabolic risk factor
27.5-29.9	4	1 (25.0%)	2 (50.0%)	3 (75.0%)
30-34.9	12	7 (58.3%)	4 (33.3%)	5 (41.7%)
≥35.0	15	8 (53.3%)	6 (40.0%)	7 (46.7%)

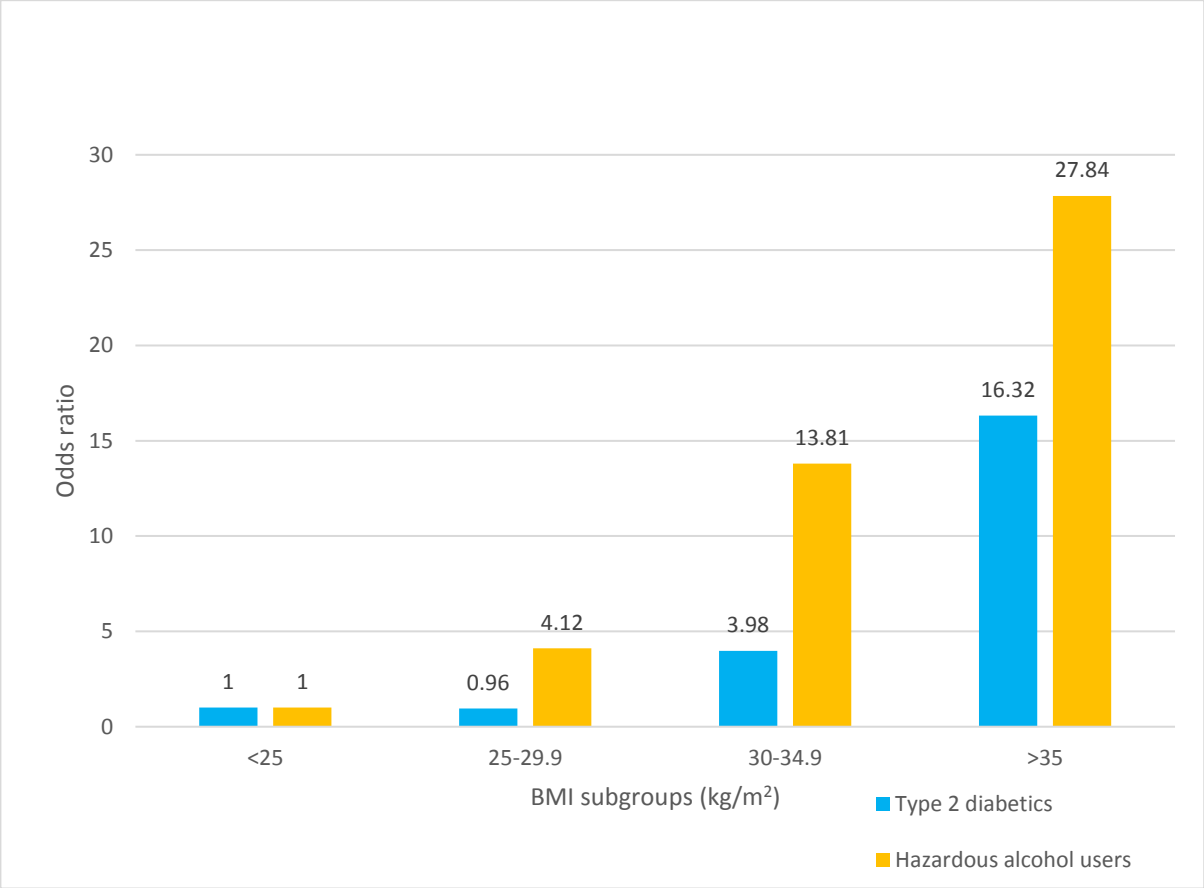
BMI = Body mass index; kPa = kilopascal; TE = Transient elastography

3.4.2.2 The effect of increasing BMI in patients with other risk factors

Combining all patients who had type two diabetes (n=151) or hazardous alcohol use (n=144) as a risk factor demonstrates the increasing odds ratios of having a TE reading ≥8.0 kPa across BMI categories (Figure 3.3). In a patient with type 2 diabetes and a BMI between 30-34.9 kg/m^2 the odds of a having a TE reading ≥8.0 kPa increased nearly fourfold (OR = 3.98, 95% CI 1.03-15.26, p value = 0.044) in comparison to a similar patient with a BMI <25 kg/m^2.

An even greater difference in odds ratios was seen across BMI categories in those patients with hazardous alcohol use as a risk factor. The odds ratio of having a TE reading ≥8.0 kPa was 13.81 (95% CI 1.47-129.90; p value = 0.002) in a patient with a BMI between 30-34.9 kg/m^2 in comparison to a patient with a BMI <25 kg/m^2.

Figure 3.3: A comparison of odds ratio for TE≥8.0 kPa per BMI categories in Type 2 diabetics (n=151) or Hazardous alcohol users (n=144)



	<25 kg/m²		25-29.9 kg/m²		30-34.9 kg/m²		≥35 kg/m²	
Risk factor	**T2DM**	**Alcohol**	**T2DM**	**Alcohol**	**T2DM**	**Alcohol**	**T2DM**	**Alcohol**
Odds ratio*	1	1	0.96	4.12	3.98	13.81	16.32	27.84
95% CI			0.24-3.71	0.43-39.66	1.03-15.26	1.47-129.90	4.03-66.02	2.37-326.20
p value			0.953	0.22	0.044	0.022	<0.001	0.008

*Adjusted for age/ gender/ ethnicity

BMI = Body mass index; kPa = kilopascal; T2DM = type 2 diabetes; TE = Transient elastography

3.4.3 Evaluating BMI as risk factor using a different non-invasive test

Of the 703 patients who attended the pathway, 548 had an extra blood test from which the ELF score could be calculated and the trend across BMI categories could be analysed. Sixty six patients (12%) had an ELF above the threshold of 9.8.

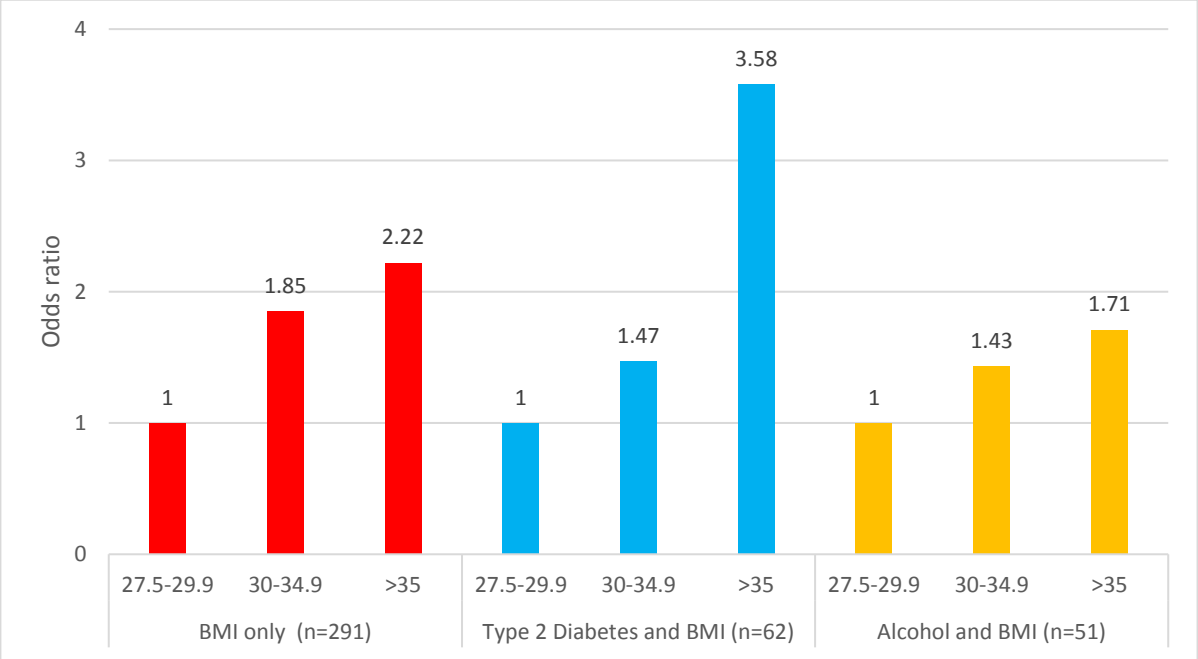
The odds of an ELF score ≥9.8 increased with increasing BMI similar to the findings observed with use of transient elastography as the risk stratification tool (Figure 3.2). In patients with a raised BMI as their only risk factor, those who had a BMI between 30-34.9kg/m^2 had an increased odds ratio of 1.85 (95% CI 0.89-3.83, p value = 0.097) of having an ELF score ≥9.8 in comparison to a patient with a BMI between 27.5-29.9 kg/m^2. Whilst in those patients with a BMI≥35 kg/m^2 the odds ratio increased further to 2.22 (95% CI 0.93-5.31; p value 0.072). This trend was again observed in those patients with dual risk factors although the findings were not statistically significant (Figure 3.4).

Combining all patients who had type two diabetes (n=119) or hazardous alcohol use (n=120) as a risk factor demonstrates the increasing odds ratios across BMI categories irrespective of which non-invasive test is used as the risk stratification tool (Figure 3.5). In a patient with type 2 diabetes and a BMI between 30-34.9 kg/m^2 the odds ratio of a having an ELF score ≥9.8 increased to 1.72 (95% CI 0.47-6.19, p value = 0.409) in comparison to a similar patient with a BMI <25 kg/m^2.

In those patients with hazardous alcohol use as a risk factor a greater difference in odds ratios was seen across BMI categories. The odds ratio of having an ELF score ≥9.8 was 6.49

(95% CI 1.39-30.17; p value = 0.017) in a patient with a BMI between 30-34.9 kg/m^2 in comparison to a patient with a BMI <25 kg/m^2.

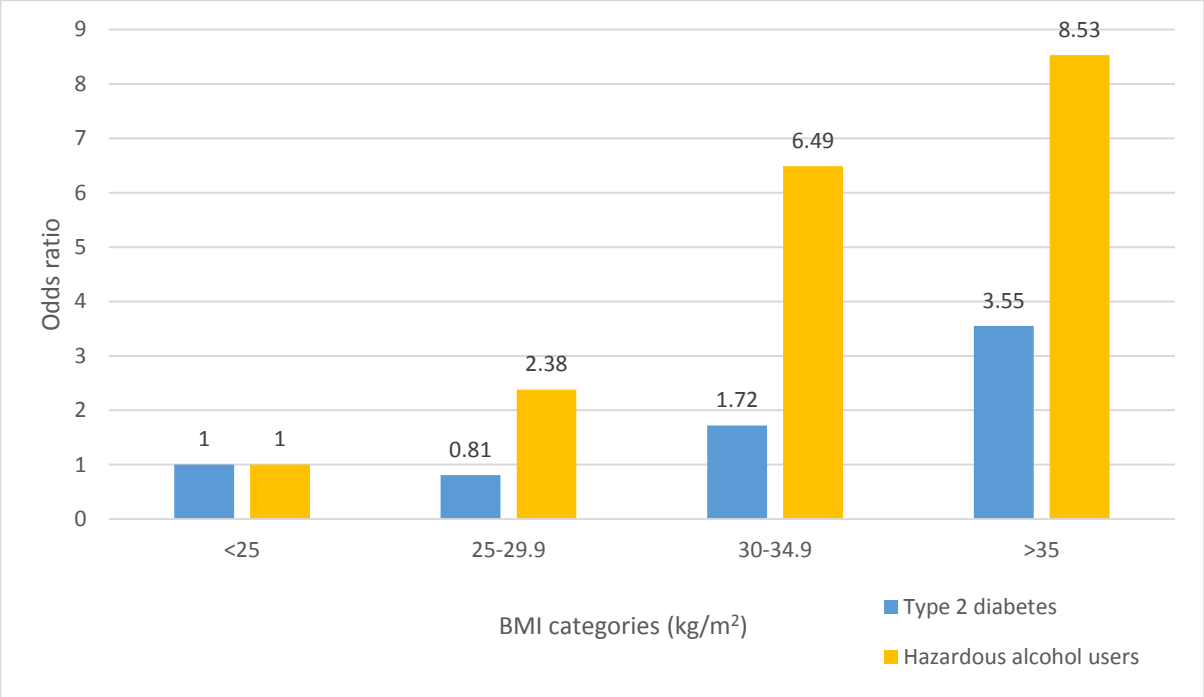
Figure 3.4: A comparison of odds ratios for ELF≥9.8 across different BMI categories according to a raised BMI (≥27.5 kg/m^2) as a single or dual risk factor



	BMI only (n=291)			Type 2 Diabetes and BMI (n=62)			Alcohol and BMI (n=51)		
BMI category (kg/m²)	**27.5-29.9**	**30-34.9**	**≥35**	**27.5-29.9**	**30-34.9**	**≥35**	**27.5-29.9**	**30-34.9**	**≥35**
Odds ratio*	1	1.85	2.22	1	1.47	3.58	1	1.43	1.71
95% CI		0.89-3.83	0.93-5.31		0.35-6.13	0.84-15.24		0.36-5.67	0.22-12.98
p value		0.097	0.072		0.594	0.084		0.607	0.604

*Adjusted for age/ gender/ ethnicity
BMI = Body mass index; ELF = Enhanced Liver fibrosis score; kPa = kilopascal

Figure 3.5: A comparison of odds ratio for ELF≥9.8 kPa per BMI categories in Type 2 diabetics (n=119) or Hazardous alcohol users (n=120)



	<25 kg/m²		25-29.9 kg/m²		30-34.9 kg/m²		≥35 kg/m²	
Risk factor	**T2DM**	**Alcohol**	**T2DM**	**Alcohol**	**T2DM**	**Alcohol**	**T2DM**	**Alcohol**
Odds ratio	1	1	0.81	2.38	1.72	6.49	3.55	8.53
95% CI			0.27-2.44	0.52-10.77	0.47-6.19	1.39-30.17	0.93-13.57	0.93-78.13
p value			0.712	0.262	0.409	**0.017**	0.064	0.058

*Adjusted for age/ gender/ ethnicity

BMI = Body mass index; ELF = Enhanced Liver fibrosis score; kPa = kilopascal; T2DM = type 2 diabetes

3.4.4 Concordance between Transient elastography and the ELF score

There is clearly a difference between the two tests with 100% concordance not seen (Table 3.9). Concordance was calculated to be 76%. However, we were unable to validate this further or determine the diagnostic accuracy of either test due to the lack of histology from a liver biopsy as the comparable gold standard.

Table 3.9: Concordance between transient elastography and ELF score

		Transient elastography (n)		
		<8kPa	**≥8kPa**	**Total**
ELF score (n)	**<9.8**	387	36	423
	≥9.8	95	30	125
	Total	482	66	548

ELF = Enhanced Liver fibrosis score; kPa = kilopascal

3.4.5 Is the transient elastography reading being falsely elevated by a raised BMI?

Transient elastography can falsely measure the subcutaneous adipose tissue which could lead to an overestimation in the number of patients with an elevated liver stiffness measurement (≥8kPa). If this was truly a problem then in the subgroup of patients who were obese one would expect a greater excess of transient elastography readings ≥8kPa in comparison to those with an elevated ELF score (≥9.8). The ELF score should not be affected by a patient's BMI.

To determine whether this could be the case a likelihood ratio test was completed between two different logistic regression models in the subgroup of patients who had an ELF score and a transient elastography reading (Table 3.9). Two exposure groups were created by stratifying patients based on whether they were obese (BMI ≥30 kg/m^2, Table 3.11) or not (Table 3.10). In the first logistic regression model an interaction parameter was included between the binary variables representing an elevated transient elastography reading and ELF score. In the second logistic regression model this interaction was not included. Stratification by BMI does give an apparently greater excess in the obese, but a likelihood ratio test between the two models did not demonstrate a significant difference (p=0.67).

Table 3.10: Concordance between transient elastography and ELF score in patients with BMI <30 kg/m^2

		Transient elastography (n)		
		<8kPa	**≥8kPa**	**Total**
ELF score (n)	**<9.8**	228 (96.6%)	8 (3.4%)	236
	≥9.8	50 (86.2%)	8 (13.8%)	58
	Total	278	16	294

ELF = Enhanced Liver fibrosis score; kPa = kilopascal

Table 3.11: Concordance between transient elastography and ELF score in patients with BMI ≥30 kg/m2

		Transient elastography (n)		
		<8kPa	**≥8kPa**	**Total**
ELF score (n)	**<9.8**	157 (84.9%)	28 (15.1%)	185
	≥9.8	45 (67.2%)	22 (32.8%)	67
	Total	202	50	252

ELF = Enhanced Liver fibrosis score; kPa = kilopascal

3.5 Discussion

3.5.1 Principal Key findings

In this community based population risk stratified for chronic liver disease, 11.7% of subjects had evidence of clinically significant liver disease (defined by a TE reading ≥8.0 kPa) highlighting the burden of undiagnosed chronic liver disease already present in our community population. The majority of patients (79.3%) with a TE reading ≥8.0 kPa did not have hazardous alcohol use as an underlying risk factor reflecting a change in the conventional risk factor profile associated with chronic liver disease.

A raised BMI (≥27.5 kg/m^2) was identified to be a significant solitary risk factor with the proportion of patients with an elevated TE reading (8%) similar to the patients with more recognised risk factors for chronic liver disease (Type 2 diabetes = 10%; Hazardous alcohol use = 3.5%). The synergism of a raised BMI in combination with other risk factors was clearly demonstrated with an increased proportion of patients identified to have an elevated TE reading (Hazardous alcohol use + BMI ≥27.5 kg/m^2 = 17.0%; Type 2 diabetes + BMI ≥27.5 kg/m^2 = 33.0%). For a TE reading ≥8.0 kPa, a rise in odds ratios was observed across increasing BMI categories within the range studied in patients who had dual risk factors and a raised BMI (≥27.5 kg/m^2) as a solitary risk factor. This trend was also observed in the subgroup of patients risk stratified by an alternative non-invasive test (ELF score ≥9.8).

A multivariate logistic regression analysis of the studied cohort demonstrated that after correcting for age, male gender and having a diagnosis of type 2 diabetes, a 1kg/m^2 increase in BMI resulted in the odds of a TE reading ≥8.0 kPa increasing by 19%.

3.5.2 Strengths and weaknesses

This is the first study assessing a raised BMI (≥27.5 kg/m^2) as a single and dual risk factor within a community based risk stratification pathway. To limit selection bias we were able to identify and invite all eligible patients from a single primary care practice coded to have the relevant lifestyle related risk factors for chronic liver disease. Use of the electronic database also allowed us to obtain detailed data regarding patient alcohol intake and their BMI; 87.7% of patients within the practice had a BMI recorded within the past 5 years. This allowed us to stratify a large well characterised community cohort using transient elastography. However, implementation of a stratification pathway based on risk factors potentially biases the outcomes that have been observed. We are unable to determine the risk of chronic liver disease within the general population or indeed within patients without any risk factors at all.

Of the patients invited to attend the pathway a response rate of 61.1% was achieved which is comparable to other community based case finding strategies for chronic liver disease [174] and better than those reported for national bowel cancer screening programmes [180]. However, there may still be a responder bias and although patient uptake between the three different risk factors was equivalent, the patients who attended may not be representative of the whole spectrum of those within the at risk groups. This may have been the case in particular for those identified to have hazardous alcohol use as a risk factor in which the proportion of those with an elevated TE reading was less than expected, although this was not statistically significant compared to the proportions observed with the other solitary risk factors. Also, identification of patients from the electronic primary care records is only as useful as the accuracy of the data recorded within it. If a patient has not been

asked about their alcohol use there will be no documentation within the electronic records from which all patients within the study were identified. This may be particularly pertinent to this study cohort in which a higher proportion of people with Asian ethnicity were living in the local area compared to the general population (22.9% vs 6.9%). Cultural differences within this ethnic group may have led to an assumption by the medical team that patients were abstinent from alcohol or if asked by their GP patients may not have declared their usage due to the stigma that could ensue.

Use of transient elastography as a surrogate marker for clinically significant liver disease could also be viewed as a limitation. Although TE has been widely tested and validated across all aetiologies and against the gold standard of a liver biopsy [110] false positives may still occur due to steatohepatitis, cholestasis, congestive cardiac failure and particularly in those patients who continue to drink alcohol [115-117]. Subsequently this may lead to an overestimation of those who have clinically significant liver disease. However a liver stiffness cut off of 8.0 kPa was used to increase the sensitivity of identifying all patients with advanced fibrosis (F3 disease) and cirrhosis (F4 disease). In patients with NAFLD a cut off of 7.9kPa has been demonstrated to have a 96.6% negative predictive value for ≥F3 disease [139].

There has also been some debate as to whether a raised BMI in itself could be interacting and falsely raise the liver stiffness measurement. Whilst studies of healthy volunteers have previously demonstrated a higher liver stiffness measurement in subjects who were obese compared to those with a normal BMI [164, 166], it must be noted that only the M probe was available in these studies. Subjects with a raised BMI are likely to have an increased skin to liver capsule distance which could result in an overestimation of their liver stiffness

measurement with this probe. In studies of cohorts with chronic liver disease, liver fibrosis has been demonstrated to be the only consistent independent variable predicting the liver stiffness measurement [139, 181, 182]. Applying an alternative risk stratification tool (ELF score ≥9.8) in our cohort demonstrated that the trend of increasing odds ratios across BMI categories is the same in all patient subgroups. This supports the argument that the results we observed with transient elastography were not fully as a result of overestimated liver stiffness measurements (false positives). We attempted to demonstrate this further by performing a likelihood ratio test between two different logistic regression models, one of which included an interaction parameter, in patients who had both risk stratification tools applied. Although this likelihood ratio test was not significant this result must be caveated by the fact that the statistical power for performing this test was low and a larger sample size is required to truly determine whether there is an interaction or not.

To identify which patients have been stratified as false positives a comparison would need to be completed against histological findings from a biopsy, which is currently considered as the gold standard although a liver biopsy in itself has its own significant limitations [98]. However, due to the ethical constraints of performing a liver biopsy in an asymptomatic community population we were not able to compare TE readings or ELF scores against histological findings. Furthermore if a liver biopsy was offered, it is unlikely that the whole cohort would have accepted this invasive test which has notable complications. Consequently the results would not have been representative of the population who have been risk stratified.

Validation of these tests in this community population is still required especially given their recent prominence within new NICE guidelines [183, 184] and that even in this small cohort

there was not 100% concordance between the two tests. This has been demonstrated in other studies [151, 185]. The only true way to determine whether these patients have been stratified correctly is to follow up this cohort for long term clinical outcomes. This would aid justification of future randomised control trials to determine whether implementation of a case finding strategy as a whole (by actively identifying patients at risk and encouraging behavioural change at an earlier time point within their natural history) has a long term effect on health outcomes or mortality.

3.5.3 Relevance to clinical practice

The rise of obesity as a metabolic risk factor is already having a demonstrable effect on the prevalence of chronic liver disease within our community population and will continue to affect the Hepatology landscape over the next 20-30 years. Twenty seven percent of the adult population in England are now reported to be obese (BMI ≥30 kg/m^2) with estimates that this will rise to 45% by 2030 [72, 186]. Yet despite many high profile public health publications [22, 25] highlighting this impact there has been no successful demonstration of strategies for reversing this trend [100]. Public health policies (e.g. fiscal measures on food manufacturers, supermarkets and a ban on advertisement to children) to address this on a population based level have so far failed to be implemented.

Within this study a raised body mass index has been highlighted as a significant independent risk factor with the burden of disease not dissimilar to other more recognised risk factors for chronic liver disease. Therefore, whilst population based interventions continue to be deliberated, large scale trials of screening for chronic liver disease which includes obesity as a single underlying risk factor should commence. In subjects with obesity, screening for

NAFLD is now supported by the European Association for the Study of the Liver (EASL) although its recommendation is to identify patients based on liver enzymes and/or ultrasound [168]. As observed in this cohort, 74.1% of patients with an elevated TE reading (≥8.0 kPa) had a normal ALT level and previously it has been shown that the sensitivity of diagnosing steatosis by ultrasound is modest until the threshold of 33% is reached [90].

Resistance to implementing case finding strategies for chronic liver disease has occurred due to concerns about which non-invasive test to use, which patients to risk stratify, the lack of effective treatments available and the cost implications [168, 187]. However, unless the Hepatology community adapt their ways of working by actively identifying cases, a vast number of patients who already have established chronic liver disease (including those with a raised BMI as their only underlying risk factor) will continue to be undiagnosed and at risk of adverse health outcomes. Whilst the case for screening is far from proven, case finding strategies to actively identify these patients will enable clinical trials to be conducted and allow therapeutic strategies for early liver disease to be tested, whether this be a trial of pharmacotherapy or the effects of encouraging behavioural change. Despite concerns about the current lack of effective treatments for patients with NAFLD, a weight loss of ≥5-10% through exercise and diet has been demonstrated to improve histological outcomes including steatosis, lobular inflammation and fibrosis [188-190]. Whilst in the UK, the National Institute for Health and Care Excellence (NICE) has recently recommended Pioglitazone, a thiazolidinedione, for NAFLD patients with advanced liver fibrosis irrespective of whether diabetes is present or not [183].

Stratifying patients at risk of liver disease will also create an opportunity for primary care physicians to identify those who would benefit from a referral to weight management

and/or alcohol misuse services and those who should be assessed for other associated health complications e.g. hypertension, hypercholesterolaemia and type 2 diabetes. Of the patients in this study who had an elevated TE reading (≥8kPa) and a raised BMI as their only risk factor, 48.4% had no other diagnosed metabolic risk factor, yet already had evidence of organ damage. Improvement in these other health outcomes that are common and have expensive complications could ensure a risk stratification pathway for chronic liver disease, which includes obesity as a risk factor, is cost effective despite the large number of individuals who would require assessment.

Whilst implementing a case finding strategy within an obese community population has now been demonstrated to be feasible and successful, further work is required to enrich the population which is stratified and increase the diagnostic yield of this approach. Including a raised BMI as an additional risk factor reduced the diagnostic yield of the current pathway with 11.7% of the study cohort having an elevated transient elastography reading (≥8kPa) compared to the 26.8% in the original pathway used by our research group [157]. However, despite a change in the risk factor profile the percentage of patients with an elevated transient elastography reading and a normal ALT was similar (74.1% in current cohort vs 72.4% in the original pathway). Also, a greater percentage of those identified to have a risk factor attended the current pathway (61.1% vs 54.8%) which may have been secondary to the change in algorithm with only one step in the pathway making it easier for patients to attend.

Being identified to have two risk factors clearly increases the likelihood of having an elevated TE reading. The synergism between hazardous alcohol use and a raised BMI has previously been demonstrated [191] with Hart *et al* [173] reporting that men who were obese and

drank >15 units of alcohol per week had an adjusted relative risk of 18.9 for liver disease mortality compared to 3.16 for those patients who drank the same amount but had a BMI <25 kg/m^2. Similarly in patients with type 2 diabetes the prevalence of NAFLD has been shown to significantly increase across greater BMI categories [192]. In addition, Harman *et al* [175] recently demonstrated that the presence of cirrhosis was significantly increased in obese patients with the additional risk factors of type 2 diabetes or hazardous alcohol use in comparison to those who were not obese (OR 9.4 and 5.6 respectively). For those with solitary risk factors, an algorithm which includes patient related factors e.g. age and gender may be more effective for patient selection rather than being identified by a risk factor alone. Whilst attempts have been made to do this previously e.g. BARD [123] / NAFLD Fibrosis score [127] these algorithms have incorporated the use of biochemical parameters, including liver function tests, which as demonstrated in this cohort are normal in the majority and should not be relied upon to identify patients at risk.

3.6 Conclusion

Obesity as a single or dual risk factor for chronic liver disease is significant and will continue to affect the Hepatology landscape over the next 20-30 years. Indeed it is already having an impact on the liver disease seen within a community population. Use of transient elastography within a risk stratification pathway is feasible and successfully identifies a significant amount of liver disease within an obese community population. However, a limitation of using transient elastography in patients with an increased BMI is the potential for a failed or unreliable reading to occur. Attempts have been made to negate this problem by developing the XL probe, as used in this study, but an inability to have access to this probe or use of the incorrect probe in an overweight patient could lead to inaccuracies in

risk stratification. Chapter 4 evaluates this further by analysing the performance of the M and XL transient elastography probes within an overweight subgroup of this study's cohort.

4 The XL probe: a luxury or a necessity? Risk stratification in an obese community cohort using transient elastography

4.1 Chapter summary

Within chapters 2 and 3 it has been demonstrated that a raised BMI is a significant risk factor for chronic liver disease. However use of transient elastography within this patient population has been independently associated with a failed or unreliable examination. Following on from the previous chapter we aimed to analyse the performance of the M and XL probes on a portable device within an overweight subgroup of the study cohort. Patients who attended the community based risk stratification pathway and were identified to have a body mass index ≥ 28kg/m^2 had a transient elastography reading with both the M and XL probes. Four hundred and seventy seven patients fitted this criteria. Twenty one percent of these patients had no valid measurements with the M probe. The XL probe significantly increased the number of valid (M vs XL probe: 66.2% vs 90.2%, p<0.001) and reliable (M vs XL probe: 77.4% vs 98.5%, p=0.028) readings that were obtained and re-stratified 5.2% of patients to have a normal transient elastography reading. Within a risk stratification pathway, the XL probe is not an optional extra, but a necessity in a population setting where a raised BMI is becoming routine.

4.2 Introduction

4.2.1 Transient elastography as a risk stratification tool

As described in the introduction of this thesis, chronic liver disease has risen up the public health agenda due to increasing mortality rates [20] and the preventable burden of disease within the general population caused in the majority by lifestyle related risk factors. Case finding strategies to tackle these issues have been suggested [168, 193] but as of yet are not routinely implemented. Yet, use of transient elastography as a risk stratification tool for liver disease has been shown to be effective as demonstrated in several studies included within the systematic review in chapter 2 [112, 113, 157] and indeed within our own pathway reported in chapter 3. Transient elastography (TE) is now recommended in guidelines by the European Association for the Study of Liver (EASL) particularly in patients at high risk of fibrosis e.g. metabolic syndrome and type 2 diabetes [193]. Advantages of transient elastography include its ease of use, provision of timely results, diagnostic accuracy, the prognostic information it provides and that it is non-invasive. With the advent of a portable machine this also allows risk stratification to occur within the community rather than a hospital setting.

4.2.2 Limitations of transient elastography in an obese population

A raised body mass index (BMI) has been independently associated with a failed or unreliable transient elastography examination using the standard 'M' probe [194-196]. Castéra *et al* [194] reviewed 13,369 transient elastography examinations using only the M probe in patients suspected to have chronic liver disease from any aetiology. A measurement failure was reported in 3.1% and an unreliable result in a further 15.8% of cases. A BMI ≥30 kg/m^2 was independently associated with both a failed (OR 7.5, 95% CI 5.6-

10.2, p=0.0001) and unreliable measurement (OR 3.3, 95% CI 2.8-4.0, p=0.0001). In a subgroup analysis of 2835 patients with the metabolic syndrome, waist circumference (≥80cm in women or ≥94cm in men) was the most significant variable associated with a failed (OR 716.3, 95% CI 5.0-52.8, p=0.0001) or unreliable examination (OR 3.0, 95% CI 2.3-3.9, p=0.0001). More recently Tapper *et al* [196] performed transient elastography using only the M probe in 164 patients proven to have non-alcoholic fatty liver disease on biopsy. The mean BMI of the cohort was 33.2 kg/m^2 and subsequently only 73.2% had a reliable liver stiffness measurement. The mean BMI in the subgroup without a reliable measurement was reported to be much higher than the group in which a measurement was obtained (37.2 kg/m^2 vs 31.8 kg/m^2) and in a multivariate analysis BMI was the only variable which was significant associated with an unreliable result. This is therefore a potential limitation of using transient elastography in a community based risk stratification pathway given the increasing proportion of the general population who are overweight or obese (65% of men and 58% of the women in England [197]) and who may be at risk of chronic liver disease and eligible for risk stratification.

4.2.3 The XL probe

The XL probe has been specifically developed by the manufacturer to be used in obese patients. Differences between the M and XL probe include the transducer diameter (7mm vs 10mm), the ultrasound frequency (3.5MHz vs 2.5 MHz) and importantly the measurement depth below the skin surface (25-65mm vs 35-75mm). This allows the elastic shear wave to be transmitted deeper into the liver parenchyma and avoids falsely measuring the subcutaneous adipose tissue which could lead to an overestimation of liver stiffness. These adaptations have been shown to significantly reduce measurement failures in an overweight population in a hospital setting [114]. Myers *et al* [114] performed transient elastography in

276 patients with chronic liver disease and a BMI ≥ 28kg/m^2 and reported the number of failures to be less frequent with the XL probe compared to the M probe (1.1% vs 16%, p<0.001) and that the XL probe was more reliable (73% vs 50%, p<0.001). The diagnostic accuracy of the probes in comparison to histological findings was similar (area under receiving operator curve: XL probe = 0.94, M probe = 0.91, p=0.28). With the recent inclusion of this probe with the portable transient elastography device this could further increase the applicability of its use within a community based risk stratification pathway.

4.2.4 Aims

The aim of this study was to analyse the performance of the M and XL transient elastography probes within a risk stratification pathway based in a community health care setting among those patients with a BMI ≥ 28kg/m^2.

4.3 Methods

4.3.1 Study approvals

Local regulatory approval was obtained from the Leicester Research Ethics Committee (13/EM/0123) and written informed consent was gained from patients. The study was performed according to the Good Clinical Practice (GCP) principals and sponsored by the University of Nottingham.

4.3.2 Study setting and patient selection

This is a prospective study which occurred alongside the study outlined in chapter 3. The study setting and patient selection have been previously described in section 3.3.2 and section 3.3.3. A transient elastography reading was attempted with both the M and XL probes in only those patients with a BMI ≥28.0 kg/m^2. This BMI cut off was selected in accordance with other studies which have evaluated the performance of transient elastography in an overweight cohort [114]. In patients who had valid readings with both probes, the M probe reading was used within the risk stratification pathway described in chapter 3.

4.3.3 Transient elastography

Transient elastography is a non-invasive diagnostic test which calculates the degree of liver stiffness by propagation of an elastic shear wave (For further details see section 1.5.1). The transient elastography device can be either static or portable but until recently the XL probe has only been available with the larger static device (Fibroscan® touch 502 (Echosens, Paris, France).

The technique for obtaining a transient elastography reading has been previously described in section 3.3.4 with differences between the M and XL probe described in the introduction of this chapter (See section 4.2.3). Ten valid measurements were collected with both the portable M and XL probes with the median value reported as the liver stiffness measurement in kilopascals (kPa). Examinations unable to record any valid readings were deemed technical failures. As an indicator of variability the ratio of the interquartile range of the liver stiffness to the median value (IQR/M) were also recorded.

The reliability of the liver stiffness measurement was initially defined by the manufacturer as the attainment of ten or more valid measurements with a success rate of ≥ 60% and an interquartile range/ median (IQR/M) ≤ 30%. However, work by Boursier *et al* [111] (See section 1.5.1) has redefined the reliability criteria and the manufacturer's recommendations have changed accordingly. Therefore, the Boursier reliability criteria [111] were specifically looked at within this part of the study (very reliable (IQR/M ≤0.1); reliable (0.10<IQR/M ≤0.30, or IQR/M >0.3 with liver stiffness measurement <7.1kPa); poorly reliable (IQR/M >0.3 and liver stiffness measurement median ≥7.1 kPa)) and compared against the manufacturers recommendations (a minimum of 10 valid measurements and an IQR/M ≤0.30 only if final liver stiffness measurement >7.1 kPa)[198]. To avoid confusion all examinations which are 'very reliable' or 'reliable' as defined by the Boursier criteria will be referred to in the subsequent text as reliable.

4.3.4 Risk stratification pathway

The risk stratification pathway has been previously outlined in section 3.3.6.

4.3.5 Statistical methods

Statistical analysis was completed using Stata version 14.2 (StataCorp LP). Baseline characteristics of the study cohort are presented as numbers (percentage) if categorical data or medians (IQR) for non-normally distributed continuous data. The Shapiro-Wilk test was used to test the normality of the data. A comparison of the performance of the M and XL probes was made using the chi squared test and the Wilcoxon signed rank test for categorical and non-normally distributed continuous data respectively.

The difference in the number of reliable and unreliable readings between the two probes using the criteria outlined by Boursier *et al* [111] and recommended by the manufacturer was compared using the chi squared test. Readings between the two probes were also compared in accordance with how this would affect risk stratification. A patient was considered to be re-stratified if the XL probe reading was <8kPa when the M probe reading had been ≥8kPa (in line with our definition of clinically significant liver disease). Correlation between the liver stiffness measurements obtained by the M and XL probes was calculated and a linear regression analysis was completed to further characterise this relationship. Multivariable regression analysis was carried out to estimate the effect of potential confounding variables. The likelihood ratio test was used to test the goodness of fit between models. Agreement between the probes was further analysed using a Bland-Altman plot. To identify variables independently associated with re-stratification univariate and multivariate logistic regression models including age, gender, BMI, Type 2 diabetes as a risk factor, Hazardous alcohol use as a risk factor, hypertension, and hypercholesterolaemia as covariates were conducted.

4.4 Results

4.4.1 Patient characteristics

The primary care practice had a total adult population of 4150 of which 1167 patients were identified to have at least one of the defined risk factors for chronic liver disease and eligible to be invited to attend the community risk stratification pathway. Of these, 703 patients attended the pathway of which 477 had a BMI ≥28.0 kg/m^2 and had attempted transient elastography readings with both the M and XL probes. The characteristics of the patients are outlined in Table 4.1. Fifty percent of the patients were male and the median age was 58 years (IQR 47-68). The majority of the patients were white (72.5%) although this was lower than the general population (87.2% in the UK) due to the high percentage of patients with Asian ethnicity (24.6%) in the community in which the risk stratification pathway was implemented. Seventy three percent of the cohort had a BMI ≥28.0 kg/m^2 as their only risk factor whilst 10.9% and 15.4% also had hazardous alcohol use or type 2 diabetes as an additional risk factor; 2.1% of patients were identified to have all three risk factors. The median BMI was 31.4 (IQR 29.4-34.7); 8.8% of patients were severely obese with a BMI ≥40.0 kg/m^2.

4.4.2 Reliability of the M and XL probes

Use of the XL probe increased the number of valid transient elastography readings (Table 4.2). At least one valid measurement was obtained for all of the patients with the XL probe whilst 21% of the patients had no valid measurements obtained with the M probe. There was a significant difference in the proportion of patients who had ≥10 valid readings

between the M and XL probes (66.2% vs 90.2%; p <0.001). Seventy six percent of the patients with <10 valid readings with the M probe had ≥10 readings with the XL probe.

Table 4.1: Baseline characteristics of the study cohort (n = 477)

Gender – Male n (%)	239 (50.1%)
Age*	58 (47-68)
Ethnicity n (%)	
White	346 (72.5%)
Asian	96 (20.1%)
Black	19 (4.0%)
Other	16 (3.4%)
Risk factor n (%)	
BMI ≥28.0 kg/m^2 only	344 (73.7%)
Hazardous alcohol use + BMI≥28.0	51 (10.9%)
Type 2 diabetes + BMI ≥28.0	72 (15.4%)
All 3 risk factors	10 (2.1%)
Metabolic risk factors n (%)	
Hypertension	192 (40.3%)
Hyperlipidaemia	112 (23.5%)
BMI (kg/m^2)	
28 – 29.9	154 (32.3%)
30-34.9	207 (43.4%)
35-39.9	73 (15.3%)
≥40	42 (8.8%)
Ischaemic heart disease n (%)	37 (7.8%)
ALT U/L*	26 (19-36)
Platelets 10^9/L*	247.5 (205-290)

* Median (IQR)

ALT = alanine aminotransferase; BMI = Body mass index

Table 4.2: A comparison in the performance of the M and XL transient elastography probes

Characteristic	M probe	XL probe	P value
≥10 valid measurements	316 (66.3%)	430 (90.2%)	<0.001
Reliable LSM* (Minimum 10 valid measurements and IQR/M <0.3 only if LSE >7.1kPa)	312 (65.4 %)	425 (89.1 %)	<0.001
Reliable LSM** (Very reliable – IQR/M ≤0.1; Reliable - 0.1<IQR/M≤0.3 or IQR/M >0.3 with LSM <7.1kPa; Poorly reliable – IQR/M>0.3 with LSM ≥7.1kPa)	369 (77.4%)	470 (98.5%)	0.028
Median success rate‡ - includes unreliable readings	100% (91-100%)	100% (100-100%)	<0.001
Median IQR/M‡	13% (9-19%)	15% (10-23%)	0.008
Median liver stiffness‡	5.3 (4.2-6.7)	4.9 (3.9-6.2)	<0.001

*In accordance with the manufacturer **Boursier *et al* 2013[111]

‡Median (IQR)

kPa = kilopascals; LSM= liver stiffness measurement

A significant difference was also seen in the reliability with >96% of patients with an unreliable M probe reading obtaining a reliable reading when the XL probe was used (Table 4.3). According to the reliability criteria outlined by Boursier *et al* [111] only 0.84% of the patients did not obtain a reliable reading with either the M or XL probe (Table 4.3). The number of reliable measurements increased with the XL probe and a significant difference was observed between the two probes (M vs XL probe: 77.4% vs 98.5%; p= 0.028). The number of unreliable readings increased with the M probe as the BMI increased (Figure 4.1). Whilst the number of unreliable readings with the XL probe remained low across all BMI categories. If reliability was defined as: ≥10 valid measurements and IQR/M < 0.3 only if the liver stiffness measurement >7.1 kPa i.e. the criteria suggested by the manufacturer, there

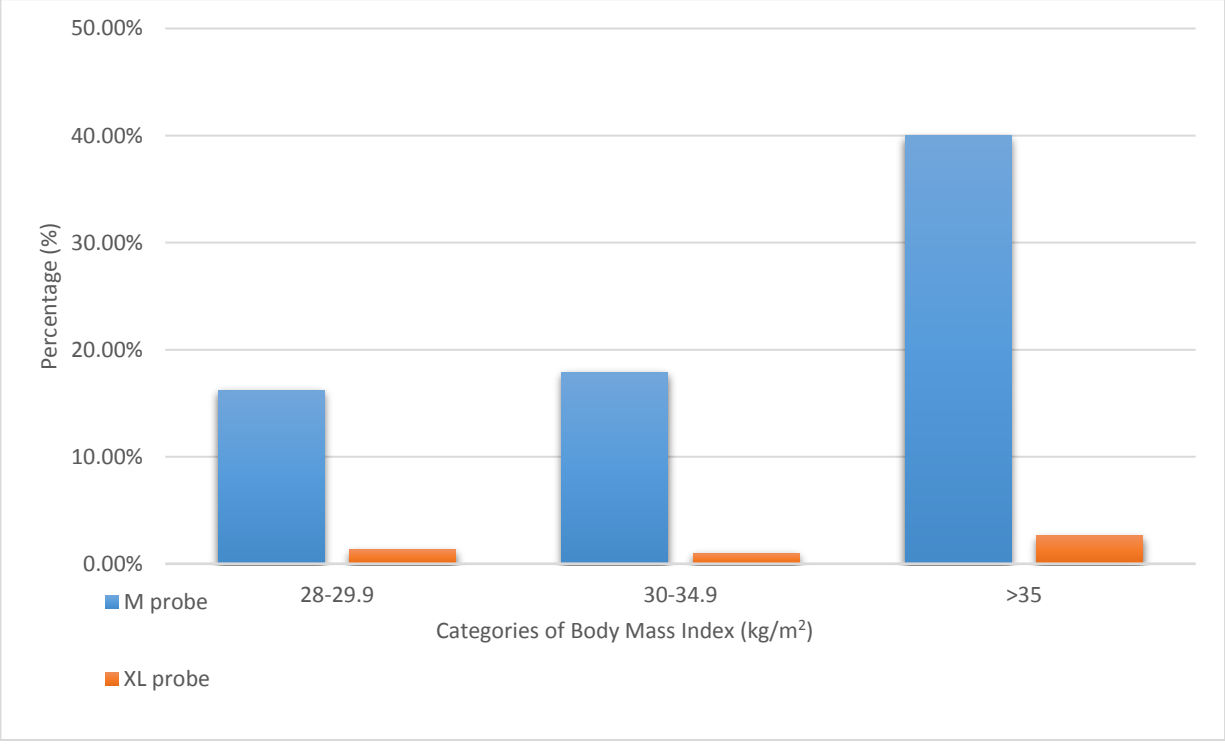
remained a significant difference between the probes (M vs XL probe: 65.4 % vs 89.1 %; p <0.001).

Table 4.3: Reliability of the M vs XL probe using Boursier criteria (n=477)

		XL	
		Unreliable	Reliable
M	Unreliable	4/108 (3.7%)	104/108(96.3%)
	Reliable	3/369 (0.8%)	366/369 (99.2%)

P value = 0.028

Figure 4.1: Percentage of unreliable readings between the M and XL probes within different BMI groups.



The transient elastography readings between the M and XL probes were highly correlated (R^2 0.78, p value <0.001) (Figure 4.2). A Bland-Altman plot (Figure 4.3) demonstrated this and revealed a larger difference at higher mean values (Pitman's test of difference in variance: r=0.656, p value = <0.001). In multivariable analysis no appreciable confounding of this relationship was found with any of the studied variables (BMI, Gender, Ethnicity, Age, Type 2 diabetes as a risk factor, Hazardous alcohol use as a risk factor). In general, the XL probe readings were lower than those obtained with the M probe with linear regression analysis returning the following estimate: XL = (0.59 x M) + 1.73. A sensitivity analysis excluding the outlier shown in Figure 4.2 (M probe reading = 75kPa) slightly diminished the correlation coefficient (R^2 0.73, p value <0.001) and altered the equation (XL = (0.72 x M) + 0.96) (Figure 4.4).

Figure 4.2: Correlation between the M and XL probes

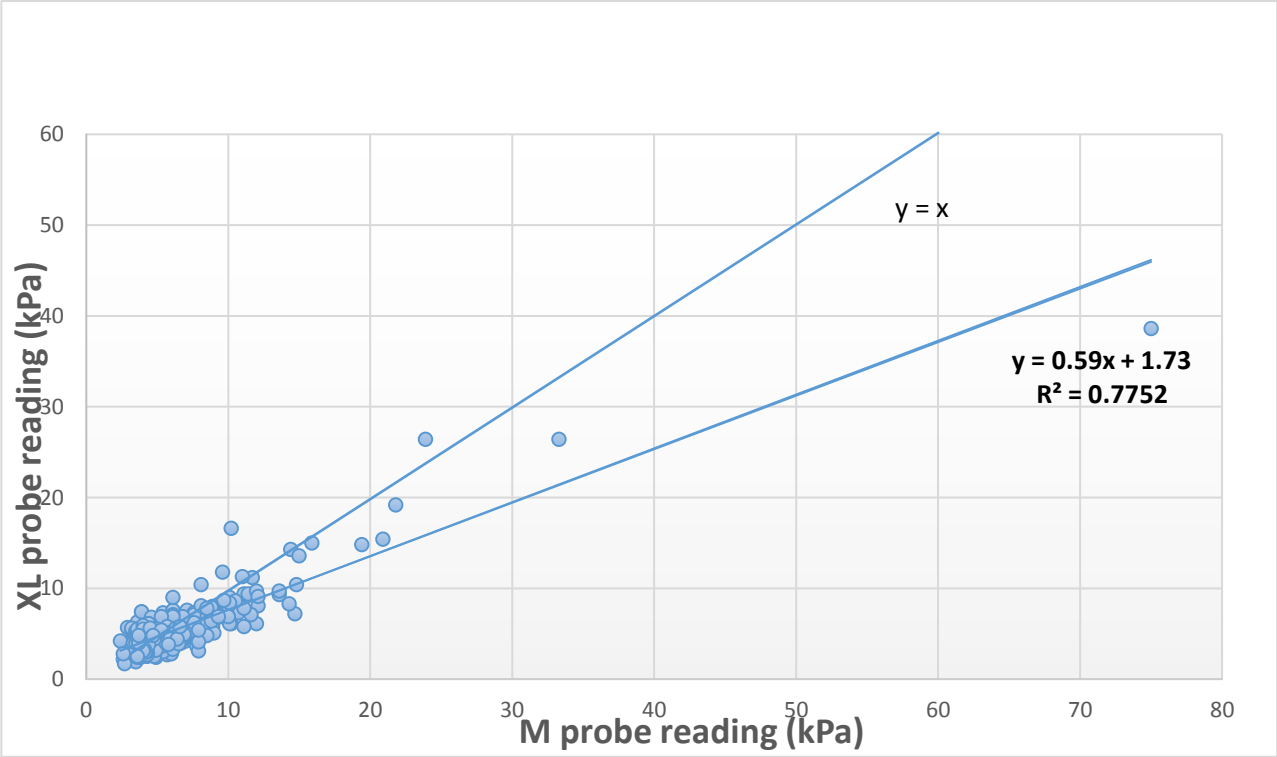
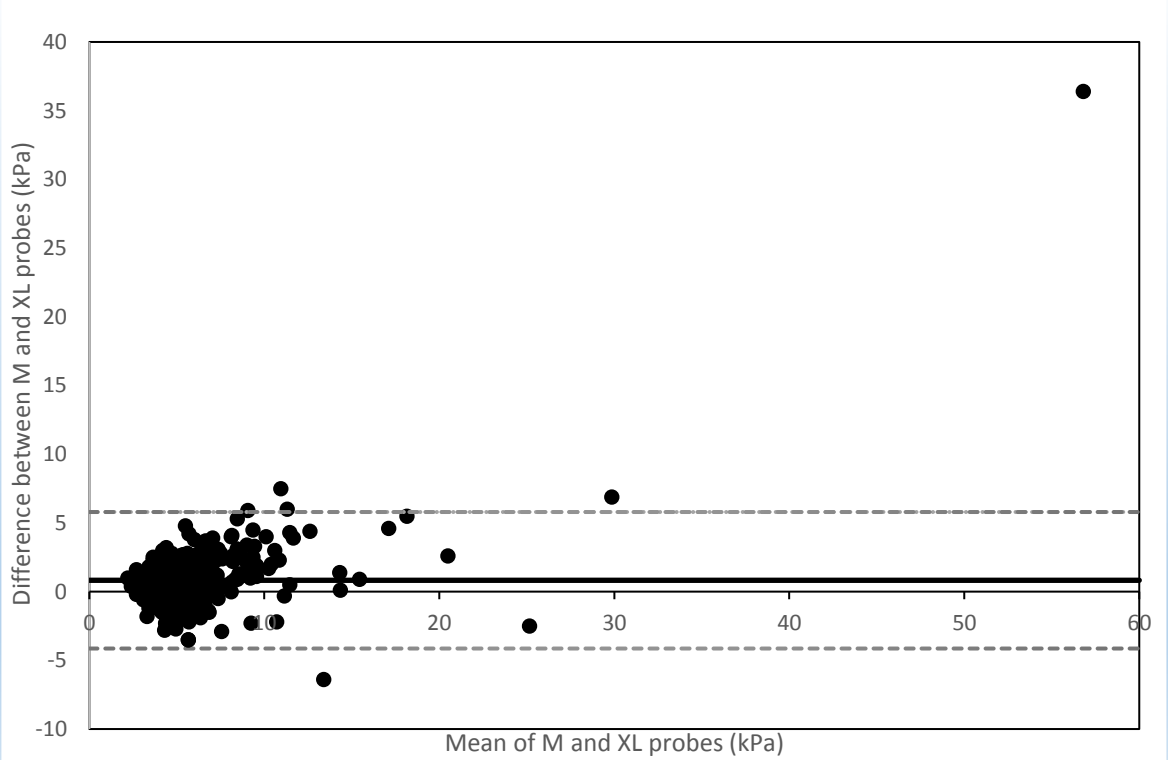
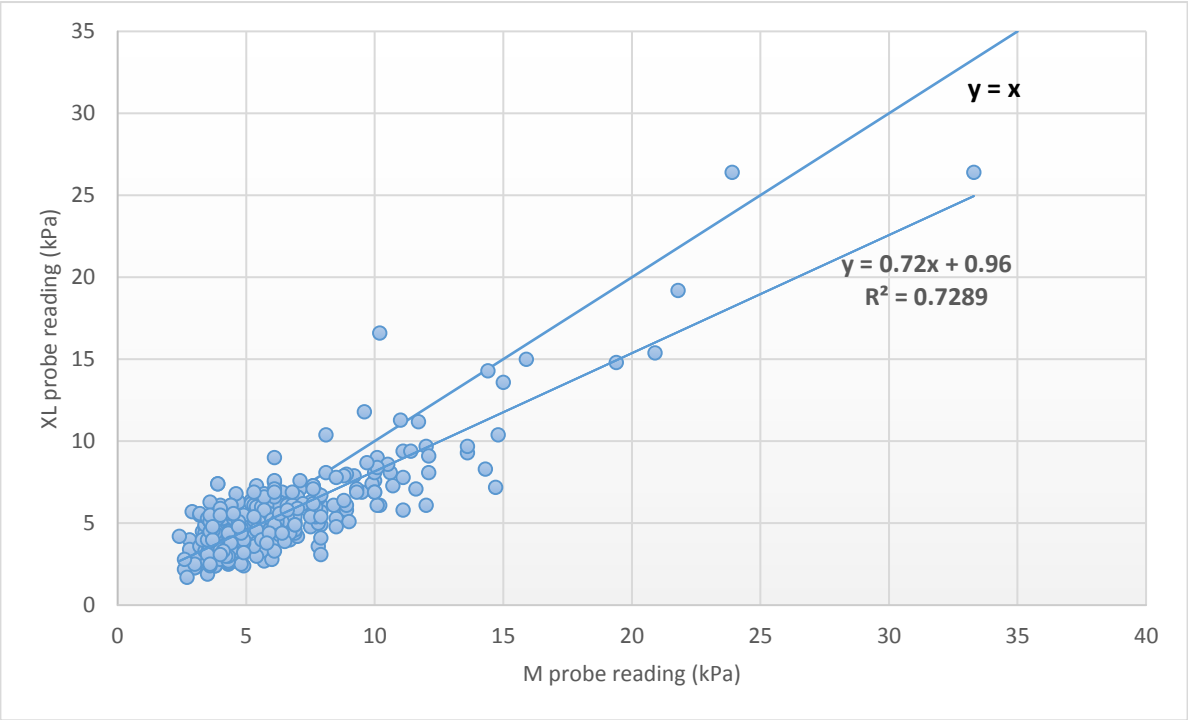


Figure 4.3: Bland Altman plot of the difference between the M and XL probe liver stiffness measurements (n=377)



The solid horizontal line equates to the mean difference between the two probes (0.82 kPa 95% CI 0.58-1.08) and the dotted lines the 95% limits of agreement (-4.14 to 5.79 kPa). The variation between the two probes is smaller at lower transient elastography readings. The difference becomes larger and more varied with higher readings.

Figure 4.4: Correlation between the M and XL probe (excluding outlier)



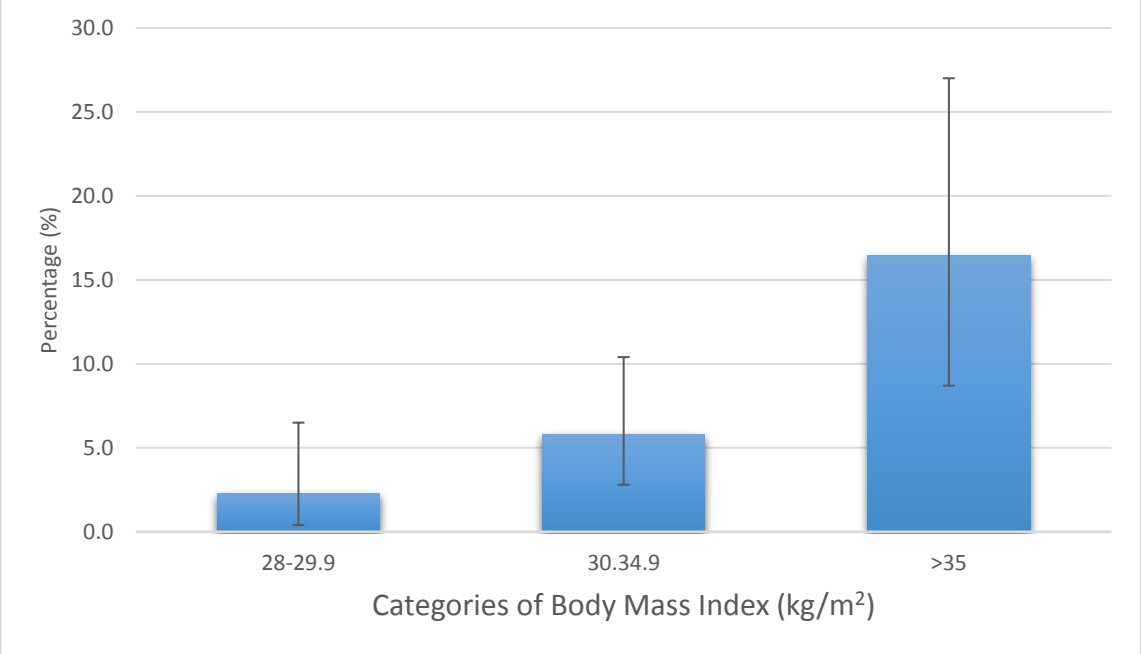
4.4.3 Use of the M and XL probes within the community risk stratification pathway

Use of the XL probe within the risk stratification pathway ensured 21% of patients obtained a transient elastography reading who otherwise would have been deemed a technical failure if only the M probe was available. The XL probe also re-stratified 5.2% of patients to have a normal transient elastography reading according to our definition for clinically significant liver disease (Table 4.4). The percentage of patients re-stratified increased as the BMI increased (Figure 4.5). BMI was the only variable in a multivariate logistic regression which was significantly associated with re-stratification. For every 1kg/m^2 increase in BMI the odds of being re-stratified increase by 19% (Table 4.5).

Table 4.4: Risk stratification of liver disease using the M and XL probes for all patients (n= 477). Includes unreliable readings.

		XL probe	
		Normal	**Clinically significant liver disease**
M probe	**No valid readings**	85 (17.8%)	15 (3.2%)
	Normal	320 (67.1%)	1 (0.2%)
	Clinically significant liver disease	25 (5.2%)	31 (6.5%)

Figure 4.5: Percentage of patients re-stratified within each BMI category



Error bars = 95% CI

Table 4.5: Univariate and multivariate logistic regression analysis of the variables associated with re-stratification

	Univariate analysis		**Multivariate analysis***	
Variable	**Odds ratio (95% CI)**	**P value**	**Odds ratio (95% CI)**	**P value**
Age	1.01 (0.98-1.03)	0.691		
Gender	0.98 (0.43-2.20)	0.957		
BMI	1.17 (1.08-1.26)	**<0.001**	1.196 (1.10-1.30)	**<0.001**
Type 2 diabetes as a risk factor for CLD	3.17 (1.33-7.55)	**0.009**		
Hazardous alcohol use as a risk factor for CLD	2.15 (0.82-5.68)	0.121		
Hypertension	2.99 (1.29-6.98)	**0.011**		
Hypercholesterolaemia	2.35 (1.03-5.39)	**0.043**		

*Adjusted for age/gender/ethnicity

BMI = Body Mass Index; CLD = Chronic Liver Disease

4.5 Discussion

4.5.1 Key findings

Within a risk stratification pathway, an ideal tool would reliably identify patients at high risk of disease and exclude those who are normal. However, as we have demonstrated use of transient elastography with only the M probe as a risk stratification tool in an obese cohort could potentially lead to a large number of patients with an invalid or unreliable transient elastography reading.

Despite 93.1% of patients who had a transient elastography reading with both probes being risk stratified equivalently, 1 in 5 patients within this obese community cohort had no valid readings with the M probe. Use of the XL probe significantly improved the number of valid and reliable transient elastography readings that were obtained. Seventy six percent of patients with <10 valid readings with the M probe had ≥10 readings with the XL probe and >96% of patients with an unreliable reading with the M probe had a reliable reading with the XL probe.

Linear regression analysis suggests there is a good correlation between the probes with the readings from the XL probe relating to that of the M probe in line with the equation (XL = (0.59x M) + 1.73). The XL probe readings are lower than those obtained with the M probe which is consistent with other findings in the literature [114, 199]. The Bland-Altman plot demonstrates this difference when using both probes in the same individual and that this difference is larger the greater the mean reading.

4.5.2 Strengths and limitations

Whilst other studies [114, 200] have compared both standard probes in a hospital setting we have demonstrated the feasibility of using both probes in the community within a risk stratification pathway. Ten valid measurements were obtained in 66.3% of patients using the M probe and in 90.2% with the XL probe. This performance compares favourably to other studies (Myers *et al* [114]: M probe = 65% XL probe = 93%; Friedrich-Rust *et al* [200]: M probe = 65% XL probe = 94%) despite being used in a community rather than a hospital setting.

The percentage of reliable readings is lower than other studies which have risk stratified using transient elastography in the community (Baba *et al* [147]: 98.3%; You *et al* [146] 97%). This is most likely due to the increased number of patients with obesity in our cohort compared to the unselected general population used within these studies. This highlights the importance of having access to the XL probe in a community setting where the prevalence of obesity is raised in order to maximise the numbers of patients who could be risk stratified.

A limitation of our study is the inability to comment on the diagnostic performance of transient elastography within this population and healthcare setting. We were unable to compare the two probe readings against histological findings although a liver biopsy does have its own documented limitations and sampling error [98]. Myers *et al* [114] analysed the performance of both transient elastography probes against histological outcomes in an overweight cohort and identified optimal liver stiffness cut offs of ≥7.8kPa with the M probe and ≥6.4kPa with the XL probe for diagnosing ≥ F2 fibrosis. It is perhaps worth noting, that

according to our equation, conversion of an M probe cut off of 7.8kPa yields an XL probe cut off of 6.3kPa which is remarkably close to the value derived by Myers *et al*.

However, it has been reported that the disparity in readings observed between the two probes is eliminated when the M probe is re-calibrated to measure a similar depth to the XL probe [114]. Similarly, when the stiffness within the liver is made homogeneous using phantom liver models the difference between the probe readings disappears [114]. Histological specimens demonstrate a greater amount of fibrous tissue around the subcapsular region which can be out of proportion to the remainder of the parenchyma [201]. This suggests therefore that the lower readings observed with the XL probe may be due to a deeper area of the liver being scanned which does not include the fibrous subcapsular tissue or the subcutaneous adipose tissue. A recent update of the instrument automatically selects the "appropriate" probe based on skin capsular distance (SCD). Our data show the difference in readings which might occur if this guidance is not followed and the incorrect probe is used which could result in overestimation of the liver stiffness measurement [114, 202]. Consequently this may cause a potential error in the risk stratification of patients despite a reliable reading being obtained. Thus choosing the correct probe is not for the sole reason of obtaining a reliable scan. Though our linear regression equation shows a clear relationship numerically between results from the two probes, it does not imply one probe can be substituted for another. The equation is skewed towards the lower readings because we have completed this study in a community setting. The relationship between the probes at higher stages of fibrosis may differ as highlighted by the Bland Altman plot and, to determine the true equation, a comparison between the probes would need to be completed in patients with more advanced disease.

At present, it is assumed that the same liver stiffness cut off can be used if the "appropriate" probe has been chosen. A validation study of the XL probe is required to ensure this assumption is correct and that the liver stiffness measurement obtained is reliable and correlates with the histological diagnosis. As we were unable to measure skin capsular distance and did not have any histological comparisons we are unable to validate the XL probe in this study but are aware of emerging evidence and await the findings with interest.

4.5.3 Relevance to clinical practice

With the global prevalence of non-alcoholic fatty liver disease now estimated to be 25% [75] and alcoholic liver cirrhosis responsible for 0.9% of deaths worldwide [30] there is an urgent need to tackle this growing epidemic and actively identity those patients who are at increased risk of liver related disease and death [61]. With new guidelines recommending screening for patients at high risk of chronic liver disease [168], tools which are accessible and easily utilised are imperative. Our results suggest that a valid and reliable M probe reading is unlikely to under estimate the degree of liver fibrosis and consequently should not mis-stratify patients who have undiagnosed clinically significant liver disease. This is supported by the close correlation observed between the results from the two probes. However, access to the M probe alone would limit the applicability of transient elastography within a community based risk stratification pathway. The adjunct of the XL probe with the portable device is an important advance to this technology to achieve a non-invasive test which can be universally applied to all patients at risk [203, 204]. Vuppalanchi *et al* [205] recently reported the results from 1,696 transient elastography examinations in 992 patients with histologically proven non-alcoholic fatty liver disease in which both the M and XL probe were available and used depending on the skin capsular distance. The mean BMI of the cohort was 33.6 kg/m^2. The failure rate based on the number of examinations was reported

as 3.2% whilst the number of unreliable exams was only 4.9%. A vast improvement from previous studies in which only the M probe was available [194, 196].

Whilst the added cost to a health care commissioner may be of concern this must be weighed up against the cost of a false positive result, a screening failure or even the cost to the health care system as a whole if the patient was to remain undiagnosed. Health economic analyses of proposed case finding strategies would be useful to determine the added economic value of having the XL probe available on a portable transient elastography device.

Even if the XL probe is accessible, there still remains uncertainty over when it should be utilised to ensure a reliable reading is obtained. The manufacturer recommends measuring the skin capsular distance (SCD) to determine which probe to use but this is not always possible in a community setting. This was indeed the case in our current study. Other studies have demonstrated a patient's BMI to be a reasonable surrogate for SCD. Our results demonstrate that 1 in 4 patients with a BMI>30 kg/m^2 had an unreliable reading with the M probe. A BMI of 30kg/m^2 could therefore be a practical threshold in which use of the XL probe should be considered ahead of the M probe. Alternatively, an argument could be made that the M probe may soon become redundant if the XL probe is able to provide more reliable readings in a general population who are increasingly overweight and at risk of chronic liver disease.

Lastly, assuming that the same liver stiffness cut off can be used for both probes, identification of the most appropriate probe would also ensure that the patient is risk

stratified correctly; 16% of patients with a BMI ≥35 kg/m^2 were re-stratified according to the XL probe reading. A failure to use the correct probe may result in patients being mis-stratified. Indeed in our own cohort 1 in 20 patients may have been risk stratified incorrectly. Importantly in the multivariable logistic regression, BMI was the only variable which was significantly associated with re-stratification. Thus, the XL probe is now not an optional extra but a necessity in a population setting where a raised BMI is becoming routine.

4.5.4 Conclusion

A reliable and valid M probe reading is unlikely to mis-stratify patients within a community based risk stratification pathway. The addition of the XL probe optimises the applicability of transient elastography within a case finding strategy by significantly increasing the number of patients with reliable readings and ensuring they are risk stratified correctly, particularly in an obese cohort. Thus in a general population where the obesity prevalence is increasing transient elastography can be accurately and reliably used as a risk stratification tool.

However, at times of constraints within the health service, both financially and in relation to resource use, a change in clinical practice must be demonstrated to ideally be cost saving and improve patient outcomes both in the short and long term. Thus far this thesis has demonstrated the applicability of implementing a case finding strategy in the community, the population which could be targeted and the risk stratification tool which can be utilised. Chapter 5 determines whether this alternative approach is ultimately cost effective.

5 Economic evaluation of a community based diagnostic pathway to stratify adults for chronic liver disease

5.1 Chapter summary

A community based risk stratification pathway using transient elastography increases the detection of clinically significant liver disease. The long-term benefits and costs of identifying patients earlier are not known. In this chapter we completed an economic evaluation to investigate the cost-effectiveness of this alternative approach compared with current standard care from an NHS England perspective. Data from the risk stratification pathway implemented by our research group was combined with Markov modelling to estimate long-term health and economic effects. The risk stratification pathway was identified to be more cost effective than standard care with a cost of £2,138 per extra quality-adjusted life-year (QALY) for patients diagnosed with non-alcoholic fatty liver disease and £6,537 per QALY for patients diagnosed with alcoholic liver disease. Incremental cost effectiveness ratios were robust and most sensitive to estimates of the rate of fibrosis progression and the effect of treatment on reducing this. The models of the risk stratification pathway demonstrated ≥85% probability of cost-effectiveness at the UK willingness-to-pay threshold of £20,000/QALY. This economic evaluation showed that implementation of a risk stratification pathway in the community is likely to be cost-effective.

5.2 Introduction

5.2.1 Chronic liver disease as a public health priority

As detailed in the introduction of this thesis liver cirrhosis is associated with increasing

morbidity and mortality and is responsible for over 1 million deaths per year worldwide [18]. The risk factors which underpin the development of chronic liver disease such as alcohol misuse, obesity and type 2 diabetes continue to rise within the general population [20, 21, 27] and thus explain why alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) are now the most common causes of chronic liver disease in the Western world. In the UK, liver disease is now a public health priority [99] with three high profile reports raising concerns about the lack of concerted action being taken to tackle the increasing rates of liver disease and the necessity of earlier detection and improved management within primary care [22, 99, 206].

5.2.2 Rationale for determining cost-effectiveness of a risk stratification pathway compared with standard care

At present, it has not been recommended to screen the general population for chronic liver disease, although within Europe liver disease mortality is comparable to other diseases which remain high upon the public health agenda [20]. However, by ensuring that those patients who are at risk of chronic liver disease are identified earlier within the natural history of the disease where implementation of lifestyle counselling, referral to specialist services and surveillance of future complications may have an impact on disease progression, there is the potential for health benefits and cost savings to occur. Therefore, a risk stratification pathway (RSP) could potentially improve quantity and quality of life for people at risk of disease, or with established but yet undiagnosed ALD/NAFLD.

As demonstrated in chapter 2 of this thesis non-invasive markers of liver fibrosis can now change how we detect liver disease. Our own research group has previously published a cross sectional study which implemented a risk stratification pathway into the community and demonstrated

an increased detection of significant liver disease using transient elastography [157]. This pathway focused on investigating patients with risk factors, including type 2 diabetes and hazardous alcohol use, rather than focusing on those with abnormal Liver function tests (LFTs). The approach of targeting specific high risk populations has been supported by EASL (European Association for the Study of the Liver) practice guidelines [207], however, as outlined by both American and European associations for the study of liver disease the cost effectiveness of this approach is still not known.

5.2.3 Aims

The overall aim was to determine the cost-effectiveness of a risk stratification pathway which targets adults in the community who have been identified to have a risk factor (type 2 diabetes or hazardous alcohol use) for developing chronic liver disease (NAFLD or ALD) compared with current standard care, from an NHS England perspective. Therefore following published economic evaluation reporting criteria [208] this aim was achieved by meeting the following objectives:

- Development of models that represent the disease and treatment pathways associated with the consequences of NAFLD and ALD in adults.
- Population of the treatment pathway models with UK relevant probabilities, utilities and resource use data for NAFLD and ALD.
- Combination of the treatment pathway models with estimates of effectiveness of the risk stratification pathway to generate probabilistic cost per quality-adjusted life-year (QALY) for NAFLD and ALD.

Separate economic models were developed for ALD and NAFLD. The overall methodology and model structure is the same but the data populating each model was specific to the underlying aetiology.

5.3 Methods

5.3.1 Modelling approach

The original cross sectional study did not allow primary observation of long term patient outcomes and incurred NHS costs resulting from consequences of implementing the risk stratification pathway. The benefits of improved patient identification and management would only be observed after several years. Therefore this study has simulated the effects of observed changes in patient identification and management on long term clinical outcomes and NHS costs.

Thus this approach combines:

I. Markov modelling of the progression of NAFLD or ALD - Identification of health states and estimates of the probability of making a transition from one state to another dependent on whether early liver disease is identified/diagnosed and treated.
II. Results of a prospective cross-sectional study of the risk stratification pathway [157] which identify the diagnostic accuracy of the risk stratification pathway and standard care.

5.3.2 Diagnosis of liver disease included within the model

Alcoholic and non-alcoholic fatty liver disease have a complex and interrelating histopathology with several features observed in both disease groups, thus at times, it is challenging to determine which risk factor is driving the disease process. In patients with multiple risk factors

a synergistic effect on liver disease mortality has been observed [172, 173]. Hart *et al* [173] demonstrated that men who drink more than 15 units per week and have a BMI of ≥ 30 have an adjusted relative risk of 18.9 for liver disease mortality compared with 3.16 for those patients who drink the same amount but have a normal weight.

For the purpose of this economic evaluation, we have simplified the complexity seen within clinical care and constructed two models as defined by:

- Alcoholic liver disease (ALD) - all patients identified to have hazardous alcohol use irrespective of whether they have an additional risk factor e.g. type 2 diabetes. Patients were identified in the feasibility study by having a Read code within the electronic GP database related to alcohol misuse, an alcohol AUDIT questionnaire score ≥ 8 [209] or documentation of an increased alcohol consumption as defined by >14 units per week for women or >21 units per week for men [157] which were the limits for safe alcohol consumption at the time of the study.

- Non-alcoholic fatty liver disease (NAFLD) - any other patient without a history of excessive alcohol use but who has been identified to have a risk factor for developing NAFLD. This includes patients with a Read code in the GP database related to Type 2 diabetes.

5.3.3 The risk stratification and standard care pathways

The risk stratification pathway (RSP) is a diagnostic algorithm (See Appendix 7.2) targeting patients in a community setting who have been identified to have a risk factor for developing chronic liver disease. This has been previously described in section 3.2.2 [157]. Briefly, patients identified with a risk factor for liver disease are invited to attend for a transient elastography

(TE) reading (previously described 1.5.1) within the community. Following a patient's transient elastography reading and the results of any further investigations a patient can be stratified to have no/mild liver disease, significant liver disease or compensated cirrhosis. A diagnosis of cirrhosis was not based on a patient's transient elastography reading alone but in combination with histology and/or endoscopic evidence of portal hypertension and/ or radiological evidence of cirrhosis or portal hypertension.

Standard care (SC) represents current diagnostic pathways used with clinical practice which rely upon abnormal liver function tests (specifically a raised alanine transaminase (ALT)) to prompt a referral to secondary care in an otherwise healthy patient with normal liver serology and no other obvious cause of disease (See Appendix 7.5).

Patients who had been risk stratified by the new and standard care pathways in the model receive interventions aimed at reducing fibrosis progression e.g. pioglitazone [183]/ brief intervention [210] which reflects best clinical practice for treatment of the underlying aetiology.

5.3.4 The study population

The population in the economic evaluation reflected the patients identified by the risk stratification pathway previously implemented by our research group and described in section 3.2.2[157]. Here, subjects were identified using a Read code in the primary care physician's electronic database related to a diagnosis of type 2 diabetes or hazardous alcohol use as previously defined. For the patients diagnosed with NAFLD, the mean (SD) age for this cohort of 293 patients was 68.4 (12.6) years. For patients diagnosed with ALD, the mean (SD) age for

this cohort of 627 patients was 43.1 (16.5) years. The initial distribution of patients was estimated based on the results of the risk stratification pathway.

5.3.5 The decision-analytic model

The decision-analytic model (Figure 5.1) was developed in collaboration with health economists from The School of Pharmacy at the University of Nottingham (Professor Rachel Elliott (RAE), Dr Lukasz Tanajewski (LH), Georgious Gkountouras (GG) and Vladislav Berdunov (VB)) using DATA Treeage version 15 software. This decision analytic model was used to describe the possible diagnostic-treatment pathways of patients being identified via the risk stratification pathway or current standard of care.

In the decision tree (Figure 5.1a), the cohort with risk factors for NAFLD/ ALD follow either the risk stratification pathway or current standard of care. The Markov model (Figure 5.1b) follows on from each of these branches. Therefore, the subsequent model pathways are the same for both the risk stratification pathway and standard care. Health states related to early liver disease which may be identified through use of the risk stratification or standard care pathway are defined as:

- No/mild disease (NMD, fibrosis stage 0 or 1)
- Significant liver disease (SLD, fibrosis stage 2 or 3)
- Compensated cirrhosis (CC, fibrosis stage 4, reflecting Baveno stage I or II [12])

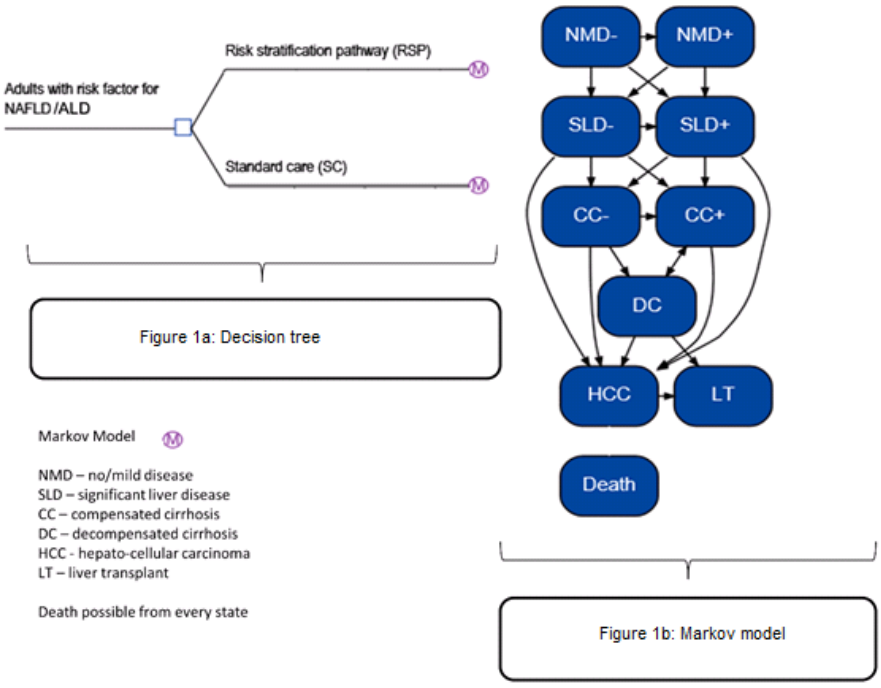
Once a patient's liver disease status is known there is a probability that interventions will be implemented to reduce risk of progression. Therefore, the probability of progressing to a subsequent stage of disease is assumed to be reduced if a patient is identified to be at risk of

developing disease (NMD+), or diagnosed with significant liver disease or compensated cirrhosis (SLD+ and CC+). This is in comparison to a patient not identified to be at risk (NMD-), or who has undiagnosed chronic liver disease (SLD- and CC-). Separate health states reflect those patients who are identified/diagnosed through the risk stratification pathway or standard care (i.e. NMD+/SLD+/CC+) and those who are not (i.e. NMD-/SLD-/CC-).

States reflecting end-stage liver disease are:

- Decompensated cirrhosis (DC)
- Hepatocellular carcinoma (HCC)
- Liver transplant (LT)
- Death

Figure 5.1: Decision tree (1a) and Markov model (1b) for the economic evaluation



A stochastic probabilistic model was developed by LH where events occur with specified probabilities. The data inputs used to populate the model provide a measure of uncertainty around the estimates, thus enriching cost-effectiveness information to decision-makers. An annual cycle length with half-cycle correction, a lifetime horizon (until 100 years of age) and the UK Treasury recommended 3.5% discount rate for costs and outcomes were used.

5.3.6 Data sources for transition probabilities, health status and resource use

An inclusive literature search was conducted by myself (Dr Rebecca Harris (RH)) in conjunction with LH, GG, VB through the electronic databases Medline, Embase and Web of Science for studies examining the natural history, treatment or resource use in managing both NAFLD and ALD. The following search terms were used: Disease progression, Fatty liver/, Liver/pathology, Liver cirrhosis/, Liver disease, alcoholic, Biopsy, Non-alcoholic fatty liver disease, Carcinoma, Hepatocellular/, Liver neoplasms/*mortality, Natural history, Survival rate, Fibrosis progression, Liver fibrosis, non-alcoholic steatohepatitis. References were limited to include humans and written in English. After excluding duplicate records, references for further evaluation were selected on title and abstract. Studies were included if they examined issues on the incidence and/or prevalence, treatment or resource use of NAFLD or ALD and its complications. Subsequently, full texts of retrieved references were evaluated and reference lists were hand-searched. Individual-patient data from the originally pathway implemented by our research group [157] was used to generate input parameters related to the population characteristics and diagnostic effectiveness of the risk stratification and standard care pathways.

Due to a paucity of data in some areas, an expert panel (Dr Neil Guha (NG), Professor Guruprasad Aithal (GA), Dr Martin James (MJ), Dr Stephen Ryder (SR), Dr Emilie Wilkes (EW)

from Nottingham University hospitals NHS Trust; Dr Toby Delahooke (TD) from University Hospitals of Leicester NHS Trust and Dr Nick Taylor (NT) from Derby Hospitals NHS Foundation Trust) was consulted to generate indicative estimates of transition probabilities and resource use.

The expert panel included regional liver specialists representing the liver centres from the East Midlands region of England that serves a population of 4.5 million people. The expert panel were invited to attend a meeting to:

- Validate the concept and structure of the health economics model
- Confirm key assumptions already created within the Markov model
- Obtain an expert opinion where no data could be identified from the scientific literature

An initial face-to-face meeting was held on Thursday 20 November 2014 with subsequent correspondence via email.

A set of key questions concerning the impact of diagnosis and management of cirrhosis on disease progression and mortality were asked from which a range of answers were obtained (See Appendix 7.6). Point estimates were calculated as the mean of estimates suggested in the responses and minimal and maximal estimates were used to generate ranges.

5.3.7 Transition probabilities

The impact of implementing the risk stratification pathway on health outcomes and costs, compared with standard care, occur as a consequence of:

(1) The increased identification rate of patients at risk of NAFLD or ALD by the risk stratification pathway (derived from the original cross-sectional study[157]), compared with standard care.

(2) The impact of earlier identification, diagnosis and treatment on disease progression. A lower probability of disease progression for NMD+/SLD+/CC+ states would occur, compared with NMD-/SLD-/CC- states.

The probability of identifying/diagnosing NMD/SLD/CC cases for the risk stratification pathway was estimated as the proportion of patients who accepted the invitation to undergo risk stratification in the study. Assuming that:

(i) The risk stratification pathway gave the true population prevalence. Since there was no gold standard diagnostic pathway to approximate true population prevalence, a patient participating in the risk stratification pathway was accurately identified/diagnosed and placed into the correct health state NMD/SLD/CC with no false positives or negatives.

(ii) The proportion of those in each disease state (NMD/SLD/CC) was the same for those who did and did not attend the risk stratification pathway. No evidence was identified to suggest that patients with asymptomatic liver disease were more or less likely to attend the risk stratification pathway compared to those without liver disease.

(iii) A patient's decision to attend the risk stratification pathway in a given year was independent of a patient's attendance in the previous years.

In the standard care pathway, the probability of identifying NMD, SLD and CC was estimated from the percentage of patients in the feasibility study who would be identified if only standard care was available i.e. patients who had a raised ALT. Assuming that:

(i) The number of patients with a raised ALT who participated in the risk stratification pathway reflected those who would be identified through the standard care pathway

(ii) The patients who did not attend the risk stratification pathway would also not have attended their GP for management under standard care

(iii) There were no false positives for standard care.

5.3.8 Utilities

Outcomes were measured in quality adjusted life years (QALYs). Age-related general population utilities from the European Quality of Life-5 Dimensions (EQ-5D) provided the baseline values, with quality of life decreasing with increasing age [211]. Utility values were given for all health states. Health status data was obtained by GG and RH preferentially from up-to-date UK sources that reflected the characteristics of the populations in the models. When this was not possible, other data sources had to be used.

5.3.9 Costs and resource use

Resource use for each health state was estimated by VB and RH based on published literature, national guidelines and international clinical practice guidelines from EASL and AASLD (American Association for the Study of Liver Disease) reflecting normal clinical practice within the UK. These estimates were checked for validity with the expert panel.

Most unit costs used were derived by VB from NHS reference costs, Personal Social Services Unit (PSSRU) and NHS pay scales [212, 213]. Where a cost could not be identified, a literature search was conducted or local finance departments were contacted by RH. All costs were inflated to the 2013/14 financial year [213]. Where a range of unit costs were available, the minimum and maximum costs were reported and included in the economic modelling. Indirect costs of illness, such as informal care, lost productivity, time expended by the patients or their carers and wider societal costs are excluded.

5.3.10 Cost-effectiveness analysis

The analysis completed by LT generated the cost per extra quality-adjusted life-year (QALY) gained by the risk stratification pathway compared with standard care. The difference in patient outcome and costs between the risk stratification pathway and standard care arms was generated. Deterministic and probabilistic incremental economic analyses were carried out. The incremental cost-effectiveness ratio (ICER) (cost per extra QALY) generated by the risk stratification pathway over standard care was calculated using the following equation:

$$ICER = (Cost_{RSP} - Cost_{SC}) / (QALY_{RSP} - QALY_{SC})$$

Where available, data were specified as distributions to fully incorporate the uncertainty around parameter values for probabilistic analysis. The analysis was run with 5000 iterations using Monte Carlo simulation to obtain point estimates and ranges of QALYs and costs generated by the risk stratification pathway or standard care arm. We report the proportion of ICER estimates in each of the four quadrants of the cost-effectiveness plane. The currently

accepted National Institute for Health and Care Excellence threshold of £20,000 per QALY gained was used to assess cost-effectiveness [214].

Many of the model parameters were subject to one-way sensitivity analysis (OSA) to determine the key drivers of the model results. The range of specific input parameters was based on alternative values identified in the literature, the upper and lower limits of confidence intervals of base-case estimates, or were arbitrary (employing expert opinions where appropriate). The intervals for deterministic OSA were chosen conservatively, to incorporate maximal level of uncertainty around point estimates. Incremental costs, QALYs, and ICERs were calculated for extreme values of the parameters, keeping all other model inputs unchanged. A Tornado diagram was presented for the parameters with the highest impact on the ICER plotting ranges for ICERs for these parameters in descending order.

To investigate the internal validity of the model along with the impact of pessimistic assumptions on the effects of identifying/ diagnosing and treating patients with chronic liver disease (NMD+/SLD+/CC+) the following multiway sensitivity analyses were conducted.

1. No effect of interventions on the progression of chronic liver disease (SLD+/ CC+) and no utility decrement for patients diagnosed with cirrhosis. This ensured internal validity of the model (incremental QALYS should be equal to 0) and an estimate of lifetime incremental cost of the risk stratification pathway compared with standard care (cost-minimisation analysis).

2. No effect of interventions used to treat patients diagnosed to have significant liver disease (SLD+) whilst the base-case effect of interventions for patients diagnosed with cirrhosis remains unchanged.

3. No effect of interventions used to treat patients diagnosed with cirrhosis (CC+) whilst the base-case effect of interventions for patients diagnosed with significant liver disease remains unchanged.

Analyses 2 and 3 were conducted with and without the utility decrement for patients diagnosed with cirrhosis.

5.4 Model inputs

5.4.1 Transition probabilities in NAFLD economic model

5.4.1.1 Annual probabilities of progression from undetected NMD- to SLD –

No studies were identified in which the probability of progression between different stages of fibrosis (F0 to F1, F1 to F2 etc.) or from health states within the model (NMD- to SLD-) were reported for NAFLD. The studies which were identified focused on long-term mortality in the NAFLD population [61] and could not be used to calculate the annual transition probabilities for fibrosis progression. The only relevant data was obtained from a study that meta-analysed the results from paired liver biopsy samples in patients with NAFLD to estimate the rate of fibrosis progression [215]. In this meta-analysis, the annual fibrosis progression rate (FPR) was calculated as the difference in fibrosis stage between the first and second biopsy divided by the time (years) between biopsies. A pooled-weighted annual FPR with 95% confidence intervals was estimated. The input parameter to the model was chosen from a subgroup within the meta-analysis (eight studies from Western countries) which was thought to be most representative of the UK population and incorporated NAFLD patients with Stage 0 fibrosis at baseline biopsy. The mean FPR was equal to 0.12 (95%CI: 0.06, 0.18) corresponding to one stage of progression over 8.3 years. In the absence of other data, this estimate was used to calculate transition probabilities between NMD-, SLD-, and CC- health states in the model in the following way:

- Time taken to progress from Stage 0 to Stage 4 fibrosis was calculated as 33.3 years where time takes to progress one stage = 1/0.12 = 8.33 years, and time to progress 4 stages = 4 x 8.33 = 33.3 years.
- In accordance with the expert panel (NG, SR, MJ, GA, EW, TD, NT) it was assumed that the

mean time taken to progress one fibrosis stage is shorter for more significant liver disease and that therefore the progression rate between fibrosis stages 0 to 4 is not linear.

- Hence, employing an exponential function (completed by LH) the following time intervals for transitions between different stages of fibrosis was derived keeping the total time taken to progress from Stage 0 to Stage 4 equal to 33.3 years:

  - **Stage 0 to 1:** 14.8 years
  - **Stage 1 to 2:** 9.2 years
  - **Stage 2 to 3:** 5.7 years
  - **Stage 3 to 4:** 3.6 years

These intervals were then used to obtain the progression rates between different stages of fibrosis assuming an initial distribution of patients between the fibrosis stages 0-4 based on the results from the risk stratification pathway (Table 5.1) and the meta-analysis by Singh *et al* [215]. The annual transition probabilities between the different health states (NMD/SLD/CC) in the model were then calculated by LH. The distribution was the same for both the risk stratification pathway and standard care cohorts. The resultant probabilities were dependent on the cycle number between the health states (Figure 5.2).

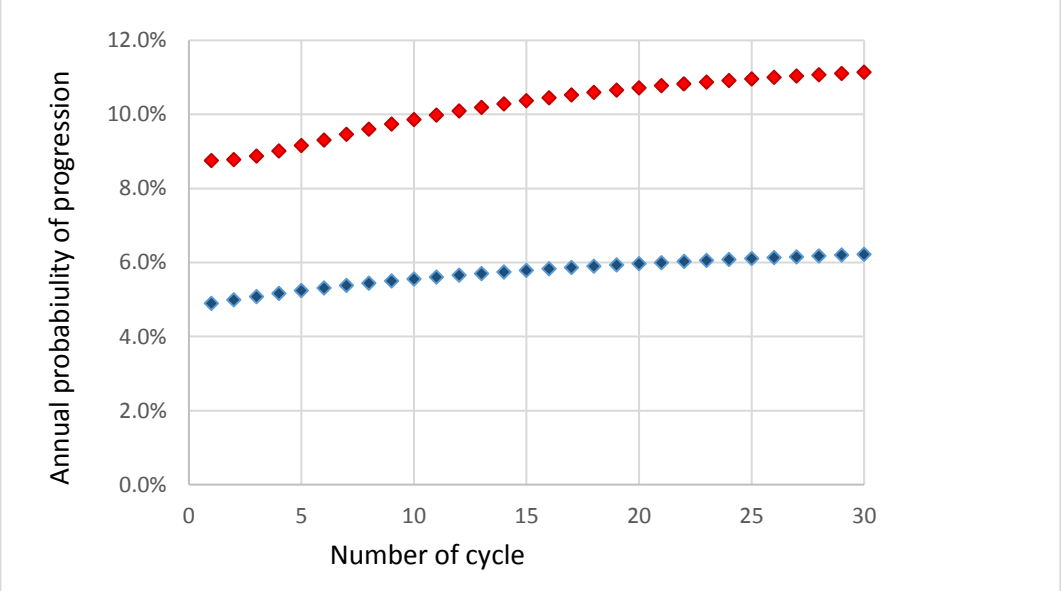
Table 5.1: Initial distribution of patients between fibrosis stages 0-4

Fibrosis stages	0	1	2	3	4	Total
% of patients in particular stage	36.2%*	32.8%	17.2%*	9.6%	4.2%	100%
Number of patients (%) **	149 (69.0%)		58 (26.9%)		9 (4.2%)	216 (100%)

*Proportion of patients with Stage 0 fibrosis in NMD and Stage 2 fibrosis in SLD (From published meta-analysis - at baseline, the distribution of fibrosis for stages 0, 1, 2, 3, and 4 was 35.8%, 32.5%, 16.7%, 9.3%, and 5.7%, respectively [215]).

**Based on study of the risk stratification pathway [157].

Figure 5.2: Annual probability of progression from NMD- to SLD, and from SLD- to CC health states



Blue = NMD- to SLD. Red = SLD- to CC. The annual probability between different health states was dependent on the fibrosis progression rates within each health state i.e. progression from NMD- to SLD was dependent on the fibrosis progression rate from F0 to F1 and F1 to F2, which

as shown above was not linear. The initial distribution of patients between the fibrosis stages was also not equivalent (Table 5.1). Therefore the annual probability varied with each cycle (1 year) of the model as the distribution of patients within each fibrosis stage changed.

5.4.1.2 Annual probabilities of fibrosis progression from NMD+ to SLD+

No data was identified to estimate of the effects of identifying/ diagnosing patients with NAFLD on the transition probabilities between the NMD, SLD and CC health states.

Despite there being many trials studying the effect of different treatments for NAFLD [216-218] these studies report a change in mean fibrosis score focusing on the impact of intervention on short-term regression or stabilisation of fibrosis rather than on the reduction in rate (or probability) of fibrosis progression. Therefore from these studies, it was not possible to calculate the transition probabilities for the progression of liver fibrosis in those patients who are diagnosed and treated.

An individual-patient dataset was obtained from a randomised controlled trial (RCT) which studied the histological effect of rosiglitazone in a NAFLD population (Fatty Liver Improvement with Rosiglitazone Therapy, FLIRT trial [219]). Sixty three patients were enrolled (32% patients had Type 2 diabetes) all of whom had a liver biopsy at baseline and at 1 year. In this study, the intervention group was offered advice on lifestyle modifications and treated with rosiglitazone while the placebo group was offer advice about lifestyle modifications only. The intervention group was assumed to be equivalent to the identified/ diagnosed arm within our model. As no specific treatment was given to the placebo group it was assumed that the fibrosis progression observed in this group would be equivalent to that seen in the unidentified/undiagnosed arm.

Using the individual-patient data from this study, patients were distributed between the three different health states within our model (NMD/SLD/CC) based upon the documented fibrosis stage at baseline and follow up at 1 year. Subsequently, the transition of patients between the health states could be observed and the effect of rosiglitazone on progression between the different health states could be calculated in relation to the placebo group who did not receive treatment. Table 5.2 and Table 5.3 summarise the transition of patients in the intervention and control groups.

Table 5.2: Number of patients who transition between NMD (fibrosis stage 0-1), SLD (fibrosis stage 2-3), CC (fibrosis stage 4) health states in the intervention group after 1 year (rosiglitazone, 32/63 patients, [37])

Patients (n)	**to NMD**	**to SLD**	**to CC**	**Total**
from NMD	8	4	0	12
from SLD	4	14	1	19
from CC	0	0	1	1
Total	12	18	2	32

Table 5.3: Number of patients who transition between NMD (fibrosis stage 0-1), SLD (fibrosis stage 2-3), CC (fibrosis stage 4) health states in the placebo group after 1 year (31/63 patients, [37])

Patients (n)	to NMD	to SLD	to CC	Total
from NMD	3	3	0	6
from SLD	6	16	2	24
from CC	0	1	0	1
Total	9	20	2	31

From the above transition matrices (ignoring regression to earlier health states) a relative risk (RR) was calculated to reflect the impact of the intervention on the progression of liver disease between NMD, SLD, and CC health states (Table 5.4):

NMD->SLD: (4/12) / (3/6) = 0.67 [RR=0.67, 95% CI: 0.21 to 2.07, p=0.7]

SLD->CC: (1/19) / (2/24) = 0.63 [RR=0.63, 95% CI: 0.06 to 6.45, p=0.7]

The RR presented here reflects the effect of early identification/diagnosis and treatment on clinically significant liver disease assuming that:

1. Lifestyle intervention is offered to all patients irrespective of whether they are identified to have clinically significant liver disease.
2. Earlier identification/ diagnosis of patients with clinically significant NAFLD leads to

treatment with a glitazone.

Rosiglitazone was withdrawn from clinical use in the UK in 2010 due to an increase in cardiovascular risk [220]. It was therefore assumed that the clinical effectiveness of rosiglitazone on the progression of liver fibrosis is similar to other glitazones (e.g. pioglitazone) as supported by published evidence [216, 221]. The first assumption makes the effect of our risk stratification pathway conservative as it may be unrealistic to assume that all patients in both the risk stratification pathway and standard care arms will be offered a life-style intervention by the GP. It is also unknown if the effect of lifestyle intervention differs depending on whether a patient is diagnosed with an invasive investigation in a hospital setting compared with a non-invasive test in the community.

In contrast, the second assumption is more optimistic as use of a glitazone is not a standard treatment for all patients with NAFLD in current clinical practice. The RCT also only studied the histological effects of treatment over 1 year and this may be too short to determine whether the subsequent effect on the progression of disease is sustained.

5.4.1.3 Annual transition probabilities from SLD (+/-) and CC (+/-) to decompensated cirrhosis, HCC, liver transplant and death

Significant liver disease to HCC

The model assumes that patients can progress from significant liver disease (SLD-/SLD+) to HCC but no data to estimate this probability was available. In a cost-utility analysis, Mahady *et al*

[221] calculated the transition probability from the combined health states of fibrosis stages 3 and 4 to HCC, based on a study of 247 NAFLD patients with fibrosis stages 3 and 4 [222] in which 52.2% had cirrhosis (stage 4). Hence, in our model we approximate the transition probability from SLD+ to HCC, assuming that the progression probability from fibrosis stage 2/3 (SLD) is similar to progression from fibrosis stage 3/4 (Table 5.4).

Significant liver disease to death

It is assumed that mortality from the health states NMD and SLD (fibrosis stages 0-3) is not increased due to liver disease. Thus an age-dependent mortality for the general population of England was assumed for the transition probability from NMD/SLD to death. To account for the increase in mortality due to the higher prevalence of type 2 diabetes within this population an excess (calculated by LH from the 10-year follow-up in United Kingdom prospective diabetes study (UKPDS) [223]) was added to general-population mortality.

Compensated cirrhosis

Progression from compensated cirrhosis (CC) through to decompensation (DC) and death were approximated based on published sources and using expert opinion (Appendix 7.6)

Results of a study by Fleming *et al* [13] based on data from the UK Clinical Practice Research Datalink (CPRD) for 4537 patients diagnosed with cirrhosis between 1987 and 2002 was used to estimate transition probabilities between stages of cirrhosis according to the Baveno classification [12]. Since there were no results reported specifically for NAFLD data the non-alcohol related cirrhosis subgroup was used which accounted for 49.2% of the cohort (viral hepatitis – 5.2%, autoimmune liver disease – 1.1%, metabolic liver disease – 7.8%, not

classified - 38.1%). Annual transition probabilities were taken from the probabilities of progression in the first year after diagnosis as annual probabilities for all years was not provided. It was assumed that these patients were diagnosed with cirrhosis (CC+). To approximate transition probabilities from undiagnosed cirrhosis (CC-) we used transition probabilities for CC+ adjusted by the responses of the expert panel (Appendix 7.6) (Table 5.4).

Compensated cirrhosis to HCC

The transition probability for compensated cirrhosis (CC+) to hepatocellular carcinoma (HCC) was reported in a cost-utility analysis [221] which was based on 3 observational studies of patients with cirrhosis [224] [225] [226]. No data for transition probabilities from undiagnosed cirrhosis (CC-) to HCC was available, so the responses from the expert panel (Appendix 7.6) were used to approximate the transition probability CC- to HCC.

Compensated cirrhosis to death

Annual transition probabilities from compensated cirrhosis to death were based on the results of the study by Fleming *et al* [13] for non-alcohol related cirrhosis. It was assumed that observed mortality was for patients diagnosed with cirrhosis (CC+). Consequently, to approximate transition probabilities from undiagnosed cirrhosis (from CC-) to death transition probabilities for CC+ were adjusted by the responses of the expert panel. (Appendix 7.6)

5.4.1.4 Transition probabilities for end stage liver disease

It is assumed that progression in end stage liver disease is not affected by the earlier diagnosis of significant liver disease or compensated cirrhosis (SLD+ and CC+) or by the earlier

identification of patients with risk factors for chronic liver disease (NMD+). The risk stratification pathway is not aimed at detecting the complications of cirrhosis hence for both the risk stratification pathway and standard care arms the transition probabilities for end stage liver disease are identical. Published studies on the natural history of end stage liver disease were used and where possible inclusion of data specific for NAFLD or non-alcohol related aetiologies (Table 5.4).

Table 5.4: Transition probabilities incorporated into NAFLD model

	Annual probability		Source
Transition	**Undiagnosed (NMD-, SLD-, CC-)**	**Diagnosed (NMD+, SLD+, CC+)**	
NMD to SLD	Dependent on cycle number (Figure 5.2)	Annual probabilities of NMD- to SLD and SLD- to CC adjusted by RR and dependent on cycle number.	[157] [215, 219]
SLD to CC			
SLD to HCC	0.4%		[221]
CC to DC*	CCI→DCIII: 7.3%; CCI→DCIV: 1.3%; CCII→DCIII: 28.5%; CCII→DCIV:8.5%	CCI→DCIII: 6.4%; CCI→DCIV:0.8%; CCII→DCIII: 17.1%; CCII→DCIV:5.1%	[13] and expert panel
CC to HCC	3.3%	3%	[221] and expert panel
NMD/SLD to death	Probability dependent on age		ONS, [157] [223]
CC to death*	CCI→death: 10.2%; CCII→death:9.0%	CCI→death: 7.5%; CCII→death: 6.6%	[13] and expert panel
DC to HCC	3%		[221]
DC to transplant	Age < 70: 5%, age ≥ 70: 0%		[221]
DC to death	DCIII→death: 25.1%; DCIV→death: 20.4%		[13]
HCC to transplant	Age < 65: 4%, age ≥ 65: 0%		[227]
HCC to death	53.0%/25.5%/17.2%/16.7% in 1^{st}/2^{nd}/3^{rd}/4^{th} year, 13.3% after 4^{th} year		[228]
Transplant to death	16.6%/3.1%/3.1% in 1^{st} /2^{nd}/3^{rd} year, 2.9% after 3^{rd} year		[229]

*I, II, III, IV refer to the Baveno stages of cirrhosis [12].
CC = compensated cirrhosis; DC = decompensated cirrhosis HCC = Hepatocellular carcinoma; NMD = No/mild disease; ONS = Office of National Statistics; RR = Relative risk; SLD = significant liver disease

5.4.2 Transition probabilities in the ALD model

5.4.2.1 Annual probabilities of progression from undetected NMD- to SLD –

No studies were identified in which the probability of progression between different stages of fibrosis (F0 to F1, F1 to F2 etc.) or from health states within the model (NMD- to SLD-) were reported for ALD. To estimate transition probabilities, data was obtained from a 4-year observational study by Mathurin *et al* [230] which reported the results of paired liver biopsies from a cohort of 193 hazardous alcohol users. Patients were classified according to their alcohol dependence status at follow up. Within each subgroup the mean follow-up fibrosis score was reported along with the mean fibrosis score at baseline (Table 5.5).

Table 5.5: Fibrosis scores within different subgroups in the study by Mathurin *et al* [230]

	Baseline assessment	**Follow-up assessments**		
		Decreased alcohol intake	**No change in alcohol intake**	**Increased alcohol intake**
Number of patients (% of the cohort)	193 (100%)	102 (53%)	41 (21%)	50 (26%)
Fibrosis score	1.06	1.6	1.76	1.84

It was assumed that the mean fibrosis progression observed within the two subgroups who i) increased or ii) did not change their alcohol intake most likely represents the natural history of fibrosis progression in those who continue to drink alcohol above the recommended weekly limits. Using this data, the rate of fibrosis progression in those patients with hazardous alcohol use as a risk factor with unidentified/undiagnosed fibrosis (NMD-/SLD-) can be calculated as detailed below.

The follow-up fibrosis score within the two subgroups who i) increased or ii) did not change their alcohol intake would be equal to:

(21%/21%+26%) x 1.76) + (26%/21%+26%) x 1.84)

(0.447 x 1.76) + (0.553 x x1.84)

= 1.804

The average time interval between the two biopsies was 3.5 years [230], thus the annual rate of fibrosis progression for undetected/ undiagnosed NMD-/SLD- health states is equal to:

(Follow up fibrosis score – baseline fibrosis score/ average time interval between liver biopsies)

(1.804-1.06)/3.5

0.744//3.5

=0.213

In the absence of other data, this estimate was used to calculate transition probabilities between NMD-, SLD-, and CC- health states in the model in the following way:

- Time taken to progress from Stage 0 to Stage 4 fibrosis was calculated as 18.8 years where time to progress one stage is 1/0.213 = 4.69 years, and time to progress 4 stages is 4 x 4.69 = 18.77 years.
- In accordance with expert opinion (NG, SR, MJ, GA, EW, TD, NT) it is assumed that the mean time taken to progress one fibrosis stage is shorter for more significant liver disease and that therefore, the progression rate between stages 0-4 of fibrosis is not

linear.

- Hence, employing an exponential function (completed by LH) the following time intervals for transitions between different stages of fibrosis was derived keeping total time taken to progress from Stage 0 to Stage 4 equal to 18.8 years:

    - **Stage 0 to 1:** 8.3 years
    - **Stage 1 to 2:** 5.2 years
    - **Stage 2 to 3:** 3.2 years
    - **Stage 3 to 4:** 2.0 years

To calculate the annual transition probabilities between the different health states (NMD/SLD/CC) the initial distribution of patients between fibrosis stages 0-4 is required. No primary care data was identified to estimate the distribution of patients between the different stages of fibrosis therefore studies of secondary care cohorts were used to calculate the average percentage of patients with particular stages of fibrosis. These were weighted by study size (Table 5.6). Although these studies are biased towards advanced fibrosis and cirrhosis (as a secondary care population is more likely to have disease compared with a primary care population) this data was used to give real life estimates for the percentage of patients with fibrosis stage 0 in NMD group (Stage 0 or 1) and the percentage of patients with fibrosis stage 2 in SLD group (Stage 2 or 3). This was agreed by NG, Dr David Harman (Clinical research fellow, DH) and RH to be a more suitable solution rather than arbitrarily defining the distribution between the different stages of fibrosis.

Table 5.6: Initial distribution of patients between stages of fibrosis 0-4 in the identified studies

Source	Number patients in study	The percentages of patients at each fibrosis stage (%)					
		Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	Total
Naveau 2009 [231]	218	7	30	22	10	31	100
Cales 2005 [232]	95	12.6	17.9	16.8	11.6	41.0	100
Nguyen-Khac 2008 [233]	103	8	18	23	19	32	100
weighted average		***8.5***	***24.3***	***21.1***	***12.6***	***33.5***	100

The percentage of patients within the health states NMD, SLD and CC are based upon the original study of the risk stratification pathway with the secondary care studies detailed in Table 5.6 used to distribute the patients within NMD and SLD health states only (Table 5.7).

Table 5.7: Initial distribution of patients between fibrosis stages 0-4

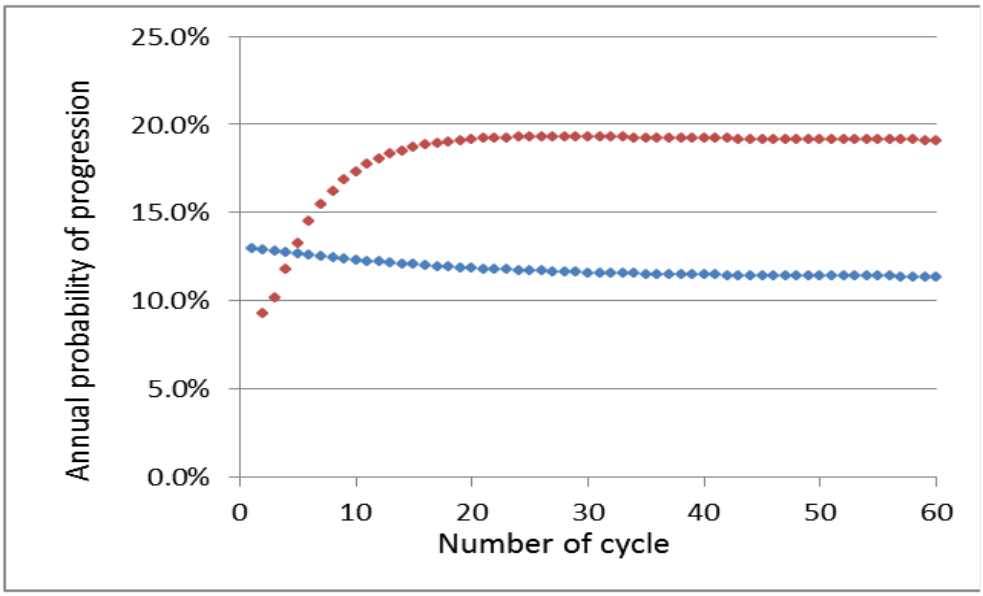
Fibrosis stages	**0**	**1**	**2**	**3**	**4**	**Total**
% of patients in particular stage	22.2%*	63.1%	8.6%*	5.1%	1%	100%
Number of patients (%) **	181 (85.3%)		29 (13.7%)		2 (1.0%)	212 (100%)

*Proportion of patients with fibrosis stage 0 in NMD and fibrosis stage 2 in SLD (Table 5.6)

**Based on study of the risk stratification pathway [157].

The time intervals were then used to obtain the progression rates between different fibrosis stages assuming an initial distribution of patients between the fibrosis stages 0-4 based on the results from the risk stratification pathway (Table 5.7). The annual transition probabilities between the different health states (NMD/SLD/CC) within the model were then calculated by LH. The resultant probabilities were dependent on the cycle number between the health states (Figure 5.3).

Figure 5.3: Annual probability of progression from NMD- to SLD, and from SLD- to CC health states



Blue = NMD- to SLD. Red = SLD- to CC. The annual probability between different health states was dependent on the fibrosis progression rates within each health state i.e. progression from NMD- to SLD was dependent on the fibrosis progression rate from F0 to F1 and F1 to F2, which as shown above was not linear. The initial distribution of patients between the fibrosis stages was also not equivalent (Table 5.7). Therefore the annual probability varied with each cycle (1

year) of the model as the distribution of patients within each fibrosis stage changed.

5.4.2.2 Annual probabilities of fibrosis progression from NMD+ to SLD+

No data was identified from the literature to estimate the transition probabilities from NMD+ to SLD+ health states. Based on the published data used in the approximation of transition probabilities from NMD- to SLD- (Table 5.5), we estimated annual transition probabilities from NMD+ to SLD+ assuming:

1. Patients who are abstinent from alcohol or who reduced their alcohol intake below the recommended weekly levels have no progression of their liver fibrosis
2. The patients identified/ diagnosed with NMD+/SLD+ receive brief alcohol intervention
3. The percentage of patients (X%) who reduce their alcohol intake sufficiently to ensure no progression in their fibrosis (1), may be approximated as the percentage of patients who have a negative alcohol use disorders identification test (AUDIT) [209] at follow up among those who had a positive AUDIT at baseline as reported in brief alcohol intervention studies [234]

Therefore X is equal to the percentage of NMD+/SLD+ patients assumed to have no fibrosis progression. Therefore the adjusted follow up fibrosis score, calculated using the data from Mathurin *et al* [230] (Table 5.5) is equal to:

(Baseline fibrosis score x % of patients who become abstinent) + (Follow up fibrosis score x % patients who continue to drink alcohol above recommended levels)

(1.06 x X%) + (1.804 x (1–X%))

$1.804 – (X\% \times 0.744)$

The change in fibrosis score between baseline and follow up is:

$1.804 – (X\% \times 0.744) – 1.06 = 0.744 \times (1–X\%)$

Assuming the time interval between the two biopsies is equal to 3.5 years as reported in Mathurin *et al* [230], the annual fibrosis progression rate is:

$((1-X\%) \times 0.744)/ 3.5 = (1-X\%) \times 0.213$

To approximate X, data was utilised from a pragmatic cluster randomised trial by Kaner *et al* [234] on the effectiveness of different brief intervention strategies aimed at reducing hazardous or harmful drinking in primary care. Three interventions were assessed: a patient information leaflet, five minutes of structured advice, and 20 minutes of brief lifestyle counselling. The results following brief lifestyle counselling were used as this was most representative of the GP service to which patients from both the risk stratification pathway and standard care arms would be referred.

Patients in the control arm were give patient information leaflets/brief advice, which would not be received by the NMD-/SLD- patients in our model as they do not accept the invitation to attend the risk stratification pathway or visit their GP as part of standard care. Therefore, the observational data from the interventional arm of this study was used to reflect the effect of

brief alcohol interventions among patients identified to be at risk (NMD+) or diagnosed with significant liver disease (SLD+).

It was assumed that the percentage of patients in the brief lifestyle counselling group with a positive AUDIT score at baseline but a negative AUDIT score at follow-up reflects the percentage of NMD+/SLD+ patients who would become abstinent or reduce their alcohol intake below the recommended weekly limit and are assumed to have no fibrosis progression (X%). Consequently, 1–X% is the percentage of patients who had a positive AUDIT score at baseline who still had a positive AUDIT score at follow-up.

Based on the results reported in the brief lifestyle counselling group [234]:

- At baseline, 249 patients had a completed AUDIT score of which 37 patients had a negative AUDIT score and 212 patients had a positive AUDIT score.
- At 12 months follow up, 203 patients had a completed AUDIT score of which 72 patients had a negative AUDIT score.
- Consequently, 35 patients with a positive AUDIT score at baseline had a negative AUDIT score at follow up (72-37 = 35) (Assuming that no patients with negative AUDIT score at baseline had a positive AUDIT score at follow up).
- It was assumed that the patients lost to follow up or with an AUDIT score missing at baseline had positive AUDIT score at follow up

Hence, the percentage of patients who would become abstinent or reduce their alcohol intake was calculated to be:

X = 35 / 212 = 0.165 (16.5%)

Therefore assuming X = 16.5%, the annual rate of progression for identified/ diagnosed health states NMD+/SLD+ is:

((1–0.165) x 0.213) = 0.178

In the absence of other data, this estimate was used to calculate transition probabilities between NMD+, SLD+, and CC+ health states in the model in the following way:

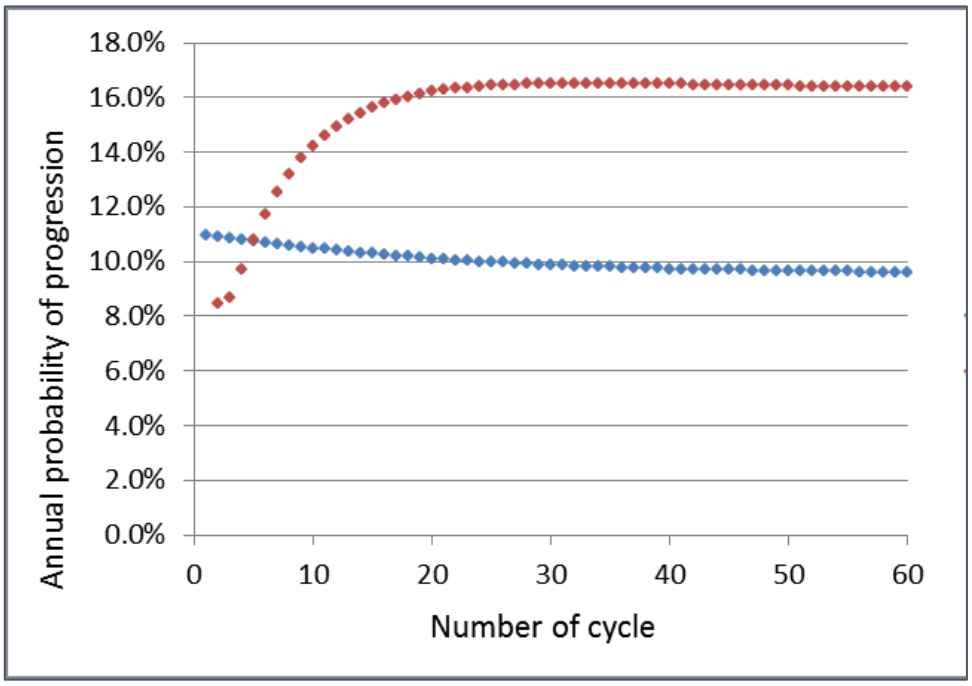
- Time taken to progress from fibrosis stage 0 to stage 4 was calculated as 22.5 years where time to progress one stage is 1/0.178 = 5.62 years, and time to progress 4 stages is 4 x 5.62 = 22.5 years
- In accordance with the expert panel (NG, SR, MJ, GA, EW, TD, NT), it is assumed that the mean time taken to progress one fibrosis stage is shorter for more significant liver fibrosis and that therefore, the progression rate between stages 0-4 of fibrosis is not linear.
- Hence, employing an exponential function (completed by LH) the following time intervals for transitions between different stages of fibrosis was derived keeping total time taken to progress from Stage 0 to Stage 4 equal to 22.5 years:

    - **Stage 0 to 1:** 10.0 years
    - **Stage 1 to 2:** 6.2 years

- **Stage 2 to 3:** 3.9 years
- **Stage 3 to 4:** 2.4 years

As previously, the time intervals were used to obtain the rates of fibrosis progression between stages 0-4 assuming an initial distribution of patients based on the results from the risk stratification pathway (Table 5.7). The annual transition probabilities between the different health states (NMD/SLD/CC) within the model were then calculated. The resultant probabilities were dependent on the cycle number between the health states (Figure 5.4). All analysis was completed by LH.

Figure 5.4: Annual probability of progression from NMD+ to SLD, and from SLD+ to CC health states



Blue = NMD+ to SLD. Red = SLD+ to CC. The annual probability between different health states was dependent on the fibrosis progression rates within each health state i.e. progression

from NMD+ to SLD was dependent on the fibrosis progression rate from F0 to F1 and F1 to F2, which as shown above was not linear. The initial distribution of patients between the fibrosis stages was also not equivalent (Table 5.7). Therefore the annual probability varied with each cycle (1 year) of the model as the distribution of patients within each fibrosis stage changed.

5.4.2.3 Annual transition probabilities from SLD (+/-) and CC (+/-) to decompensated cirrhosis, HCC, liver transplant and death

Significant liver disease to HCC

The model assumes that patients can progress from significant liver disease (SLD-/SLD+) to HCC. We approximated this probability as being the same for both health states since no data was identified on the effect of diagnosing patients with significant liver disease and the subsequent development of HCC. The transition probability from SLD-/SLD+ to HCC was calculated to be the same as compensated cirrhosis to HCC [235] adjusted by the standardized incidence ratio estimated in a large prospective study [236]. This therefore reflects how HCC development is less likely for a patient with significant liver disease compared to a patient with cirrhosis (Table 5.8).

Significant liver disease to death

It is assumed that mortality in the health states NMD and SLD (fibrosis stages 0-3) is not increased due to liver disease at this stage. Thus an age-dependent mortality for the general population of England was assumed for the transition probability from NMD/SLD to death.

Compensated cirrhosis

Progression from compensated cirrhosis (CC+) through to decompensation (DC) and death were estimated based on published sources and using the expert panel (Appendix 7.6).

Results from Fleming *et al* [13] based on data from CPRD for 2307 patients diagnosed with alcoholic cirrhosis between 1987 and 2002 was used to estimate transition probabilities according to the Baveno classification[12]. Annual transition probabilities were taken from the probabilities of progression in the first year after diagnosis as data on annual probabilities for all years was not provided. It was assumed that these patients were diagnosed with cirrhosis (CC+). To approximate transition probabilities from undiagnosed cirrhosis (CC-) we used transition probabilities for CC+ adjusted by the responses of our expert panel. (Appendix 7.6) (Table 5.8).

Compensated cirrhosis to HCC

The transition probability from compensated cirrhosis to hepatocellular carcinoma was estimated from a cohort study conducted between 1993 to 2005 of all Danish citizens with a first-time hospital diagnosis of alcoholic cirrhosis [235]. In this cohort of 8482 patients, HCC incidence starting 1 year after diagnosis of alcoholic cirrhosis through to the year 2009 was reported and used within the model (Table 5.8)

Compensated cirrhosis to death

Annual transition probabilities from compensated cirrhosis to death were based on the results of the study by Fleming *et al* [13] for alcohol related cirrhosis. It was assumed that observed

mortality was for patients diagnosed with cirrhosis (CC+). Consequently, to approximate transition probabilities from undiagnosed cirrhosis (from CC-) to death transition probabilities for CC+ were adjusted by the responses of the expert panel. (Appendix 7.6).

5.4.2.4 Transition probabilities for end stage liver disease

As with the NAFLD model, it is assumed that progression in end stage liver disease is not affected by the earlier diagnosis of significant liver disease or compensated cirrhosis (SLD+ and CC+) or by the earlier identification of patients with risk factors for chronic liver disease (NMD+). Therefore, the transition probabilities for end stage liver disease are identical for both the risk stratification pathway and standard care arms. Published studies on the natural history of end stage alcoholic liver disease were used (Table 5.8).

Table 5.8: Transition probabilities incorporated into ALD model

	Annual probability		**Source**
Transition	**Undiagnosed** **(NMD-, SLD-, CC-)**	**Diagnosed** **(NMD+, SLD+, CC+)**	
NMD to SLD	Dependent on cycle number (Figure 5.3) incorporating fibrosis progression rate of 0.213	Undiagnosed adjusted by effect of brief alcohol intervention on fibrosis progression = 0.178 (95%CI: 0.167 to 0.188). Dependent on cycle number (Figure 5.4)	[230] [231-233] and RSP study [157]
SLD to HCC	0.04%		[235] [236]
CC to DC*	CCI→DCIII: 2.8%; CCI→DCIV: 2.7%; CCII→DCIII: 30.9%; CCII→DCIV: 16.5%	CCI→DCIII: 24.1%; CCI→DCIV:1.5%; CCII→DCIII: 17.4%; CCII→DCIV: 9.3%	[13] and expert panel

CC to HCC	0.44%	0.4%	[235]
NMD/SLD to death	Probability dependent on age		ONS (life tables), RSP study [157]
CC to death*	CCI→death: 12.0%; CCII→death: 11.3%	CCI→death: 7.0%; CCII→death: 6.6%	[13] and expert panel
DC to HCC	2.3%		[237]
DC to transplant	Age < 70: 5%, age ≥ 70: 0%		[221], based on [238]
DC to death	DCIII→death: 16.4%; DCIV→death: 16.5%		[13]
HCC to transplant	Age < 65: 4%, age ≥ 65: 0%		[227]
HCC to death	53.0%/25.5%/17.2%/16.7% in $1^{st}/2^{nd}/3^{rd}/4^{th}$ year, 13.3% after 4^{th} year		[228]
Transplant to death	16.6%/ 1^{st} year, 3-6% after 1^{st} year		[239]
*I, II, III, IV refer to the Baveno stages of cirrhosis [12]. CC = compensated cirrhosis; DC = decompensated cirrhosis HCC = Hepatocellular carcinoma; NMD = No/mild disease; ONS = Office of National Statistics; RR = Relative risk; SLD = significant liver disease			

5.4.3 Incorporating the effect of the risk stratification pathway (NAFLD and ALD) into transition probabilities

There is currently no comparative study that provides evidence for the effectiveness of the risk stratification pathway in NAFLD or ALD. The probabilities of diagnosing significant liver disease or compensated cirrhosis (SLD+ and CC+) and identifying patients at risk with no/mild disease (NMD+) have been estimated for the risk stratification pathway and standard care arms from

the data collected in the original study [157] assuming that:

(1) If a patient participates in the risk stratification pathway they are accurately identified/diagnosed and stratified into the correct health state. Therefore there are no false positives or negatives. Since the risk stratification pathway is the first to be implemented in a community setting to detect significant liver disease or compensated cirrhosis (SLD+/CC+), or those who are at risk of developing disease (NMD+), there is no gold standard diagnostic pathway to approximate the true population prevalence. Hence, the risk stratification pathway is assumed to give the true population prevalence.

(2) There are no false positives for standard care.

(3) The percentage of patients who do not participate in the risk stratification pathway will be the same as the study. In the NAFLD model, 26.3% of patients with type 2 diabetes did not accept an invitation to participate within the risk stratification pathway. In the ALD model, 66.2% of patients with hazardous alcohol use as a risk factor did not accept an invitation to participate within the risk stratification pathway.

(4) Among the patients who did not attend the proportion of those with disease is assumed to be the same as those who did participate. This assumption is reasonable as patients with asymptomatic liver disease are not more or less likely to attend compared to those without disease.

(5) The percentage of NMD, SLD, and CC patients who would be identified if only standard care was available was calculated based on the number of patients with a raised ALT who participated in the risk stratification pathway (Table 5.9, Table 5.10).

(6) The patients who did not participate in the risk stratification pathway would also not have attended their GP for management under standard care.

(7) A patient's participation in the risk stratification pathway in a given year (determining the probability of NMD/SLD/CC detection for the risk stratification pathway and affecting the probability of detection for standard care) is assumed to be independent of a patient's previous decision to participate.

Table 5.9: The probability of identifying/detecting NMD/SLD/CC cases: NAFLD model

Probability of:	**RSP**	**SC****
identifying NMD	73.7%*	2.0%
detecting SLD	73.7%	16.5%
detecting CC	73.7%	8.2%

Source: RSP study [157] – 293 patients had type II diabetes as a risk factor for developing NAFLD.

*73.7% =216/293 – patients who attended the risk stratification pathway. Notice that assumptions (1), (3), and (4) lead to the same probability of identification/detection of NMD, SLD and CC which is equal to the percentage of patients attending the risk stratification pathway.

**Percentage of patients detected by the risk stratification pathway who would also have been detected through standard care i.e. patients with a raised ALT level.

Table 5.10: The probability of identifying/detecting NMD/SLD/CC cases: ALD model

Probability of:	**RSP**	**SC****
identifying NMD	33.8%*	1.5%
detecting SLD	33.8%	5.8%
detecting CC	33.8%	0%

Source: RSP study [157] – 627 patients had hazardous alcohol use as a risk factor for developing ALD.

*33.8% =212/627 – patients who attended the risk stratification pathway. Notice that assumptions (1), (3), and (4) lead to the same probability of identification/detection of NMD, SLD and CC which is equal to the percentage of patients attending the risk stratification pathway.

**Percentage of patients detected by the risk stratification pathway who would also have been detected through standard care i.e. patients with a raised ALT level.

5.4.4 Utilities

5.4.4.1 NAFLD model

No studies reporting utilities for NAFLD health states were identified. Based on expert opinion (RH, NG, and DH) it was assumed that health-related quality-of-life (QoL) data for NMD, SLD and for CC- may be approximated by using QoL data available for a population with type 2

diabetes. For CC+, a utility decrement was included to capture psychological effects of diagnosis. Data on QoL reported in Health Survey for England [240] and results from the risk stratification pathway [157] were used to calculate age-dependent utility for NMD, SLD, and CC health states (i.e. employing the regression equation that estimated EQ-5D utility scores dependent on age and other covariates [240]). Data on demographics and the prevalence of co-morbidities in the target population (Obesity 47.4%, hypertension 63.5%) [157] were also applied to calculate utilities attached to the model's states. For DC, HCC and liver transplant health states, utility data were taken from a study based on patients with HCV [241] (Table 5.11)

Table 5.11: Utility data incorporated into the NAFLD model

Health State	Utility value	Source
NMD, SLD, CC-	0.88-0.91	[240] [157]
CC+	0.78-0.81	[240] [157] [221]
DC	0.66 (95 % CI: 0.46–0.86)	[241]
HCC	0.65 (95% CI: 0.44–0.86)	
Liver transplant	0.69 (95% CI: 0.62–0.77)	
Death	0	

5.4.4.2 ALD model

No studies reporting utilities for health states within the ALD model were identified. Based on expert opinion (RH, NG, DH) and given that patients in health states NMD, SLD, CC- are generally asymptomatic, health-related quality-of-life (QoL) data for these health states was approximated using QoL data from a primary care population who were identified to have

hazardous or harmful drinking [37]. Utilising population data from the study of the risk stratification pathway (Obesity 47.4%, hypertension 63.5%, type 2 diabetes 8%) the regression equation to approximate EQ-5D utility score [240] was applied to estimate age-dependent utility for NMD, SLD, and CC- health states. The utility decrement for CC+ and utility values for DC, HCC, and transplant were the same as the NAFLD model (Table 5.12).

Table 5.12: Utility data incorporated into the ALD model

Health State	**Utility value**	**Source**
NMD, SLD, CC-	0.81-0.75	[240], [234], [157]
CC+	0.71-0.65	[240], [234], [157], [221]
DC	0.66 (95 % CI: 0.46–0.86)	[241]
HCC	0.65 (95% CI: 0.44–0.86)	
Liver transplant	0.69 (95% CI: 0.62–0.77)	
Death	0	

5.4.5 Resource use and costs for both NAFLD and ALD models

For patients identified to be at risk or diagnosed with chronic liver disease, costs for the NMD+/SLD+/CC+ health states differ between the risk stratification pathway and standard care arms due to a difference in the diagnostic investigations and therapeutic interventions which occur (Table 5.13, Appendix 7.7). There is also a difference in resource use between the first and subsequent years of the pathway due to a change in focus from initial diagnosis to monitoring disease progression and implementation of surveillance strategies. Further detailed information can be found in Appendix 7.7). It was assumed that patients who are

unidentified or undiagnosed (NMD-/SLD-/CC-) accrue no costs in either of the risk stratification pathway or standard care arms.

Table 5.13: Annual costs (ranges) for the NAFLD and ALD models (£)

		NAFLD		ALD	
Health state	**Pathway ***	**1st year**	**subsequent year**	**1st year**	**subsequent year**
NMD	**RSP**	183	158	862	578
	SC	1223	65	1902	0
SLD	**RSP**	1219	363	2087	971
	SC	1223	368	2091	976
CC	**RSP**	1721 (1651-1791)[a]	921 (887-956)[a]	2419 (2350-2489)[a]	1361 (1326-1396)[a]
	SC	1725 (1656-1795)[a]	884 (850-919)[a]	2424 (2355-2494)[a]	1323 (1289-1358)[a]
DC		6672 (4221-9123)[ab]	7706 (5525-9887)[ab]	7398 (4947-9849)[ab]	8172 (5991-10354)[ab]
HCC		19414 (19151-19678)[b]	18172 (17909-18436)[b]	19414 (19151-19678)[b]	18172 (17909-18436)[b]
Transplant		89282 (56301-184574)[c]	20687 (15549-25452)[c]	89282 (56301-184574)[c]	20687 (15549-25452)[c]

*Annual costs for NMD, SLD, and CC states are different for the RSP and SC.

[a] Interval based on cost of OGD: refer to Appendix 7.7

[b] Interval based on uncertainty regarding secondary care resource use: refer to Appendix 7.7

[c] Range of estimates derived from studies of the cost of the transplant and follow-up care in first year: refer to Appendix 7.7

5.5 Results: Cost effectiveness of the risk stratification pathway versus standard care in NAFLD

5.5.1 Base-case analysis

Deterministic cost-effectiveness analysis derived a mean lifetime cost per patient of £9,017 for the risk stratification pathway and £8,505 for standard care. Mean QALYs generated was 8.49 for the risk stratification pathway and 8.25 for standard care. Incremental cost was £512 and incremental QALY was 0.24, providing an ICER of £2,138 per extra QALY gained for the risk stratification pathway compared with standard care (Table 5.14).

Table 5.14: Cost-effectiveness analysis of RSP vs SC: base case scenario, NAFLD model

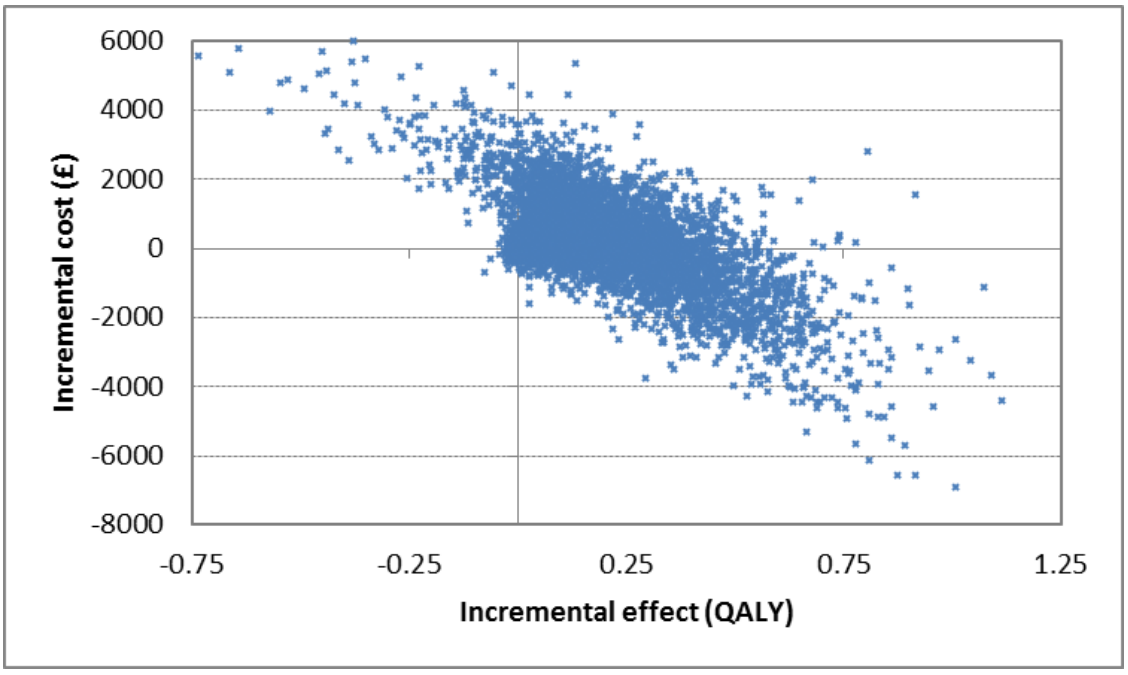
<table>
<tr><th colspan="6">Deterministic results, means</th></tr>
<tr><th></th><th>Cost (in £)</th><th>Incremental cost (£) RSP vs. SC</th><th>QALY</th><th>Incremental QALY RSP vs. SC</th><th>ICER (£/QALY)</th></tr>
<tr><td>RSP</td><td>9,017</td><td rowspan="2">512</td><td>8.49</td><td rowspan="2">0.24</td><td rowspan="2">2,138</td></tr>
<tr><td>SC</td><td>8,505</td><td>8.25</td></tr>
<tr><td colspan="6">Probabilistic sensitivity analysis results, means (2.5%, 97.5% percentiles)</td></tr>
<tr><td>RSP</td><td>10,307 (3,811; 20,442)</td><td rowspan="2">225 (-2,699; 2,856)</td><td>7.93 (2.80;11.09)</td><td rowspan="2">0.21 (-0.1; 0.65)</td><td rowspan="2">-1,010* (-40,583; 50,023)</td></tr>
<tr><td>SC</td><td>10,082 (3,494; 20,793)</td><td>7.72 (2.78;10.67)</td></tr>
</table>

* RSP dominated by SC (NW quadrant): 5.8%; SC dominated by RSP (SE quadrant): 37.1%; NE quadrant: 56.3%; SW quadrant: 1.0%

In the probabilistic cost-effectiveness analysis, mean lifetime cost per patient (2.5% and 97.5% percentiles) were £10,307 (£3,811; £20,442) and £10,082 (£3,494; £20,793) for the risk stratification pathway and standard care respectively. Mean QALYs generated per patient

(2.5% and 97.5% percentiles) were 7.93 (2.80; 11.09) for the risk stratification pathway and 7.72 (2.78; 10.67) for standard care. Incremental cost and QALYs were £225 (-2,699; 2,856) and 0.21 (-0.1; 0.65), respectively. The ICER (2.5%, 97.5% percentiles) was -£1,010 (-£40,583; £50,023). There was a 37% probability that the risk stratification pathway dominated standard care and an 85% probability that the risk stratification pathway was cost-effective at the UK willingness-to-pay threshold of £20,000/QALY (Table 5.14 and Figure 5.5).

Figure 5.5: Probabilistic sensitivity analysis: cost-effectiveness plane, NAFLD model



The horizontal axis represents the difference in effect between the RSP and standard care. The vertical axis represents the difference in cost. This divides the plane into four quadrants. In the North West (NW) quadrant the RSP is more costly and less effective i.e. the RSP is dominated by SC. In the South East (SE) quadrant the pathway is less costly and more effective i.e. SC is dominated by the RSP. In the North East (NE) quadrant the RSP is more costly but more effective and choice depends on the cost effectiveness ratio one is willing to accept. In the South West (SW) quadrant the RSP is less costly but less effective than SC and

would therefore not be accepted. The results within each quadrant are as follows: NW quadrant = 5.8%. SE quadrant = 37.1%. NE quadrant = 56.3%. SW quadrant = 1.0%.

5.5.2 One-way sensitivity analyses

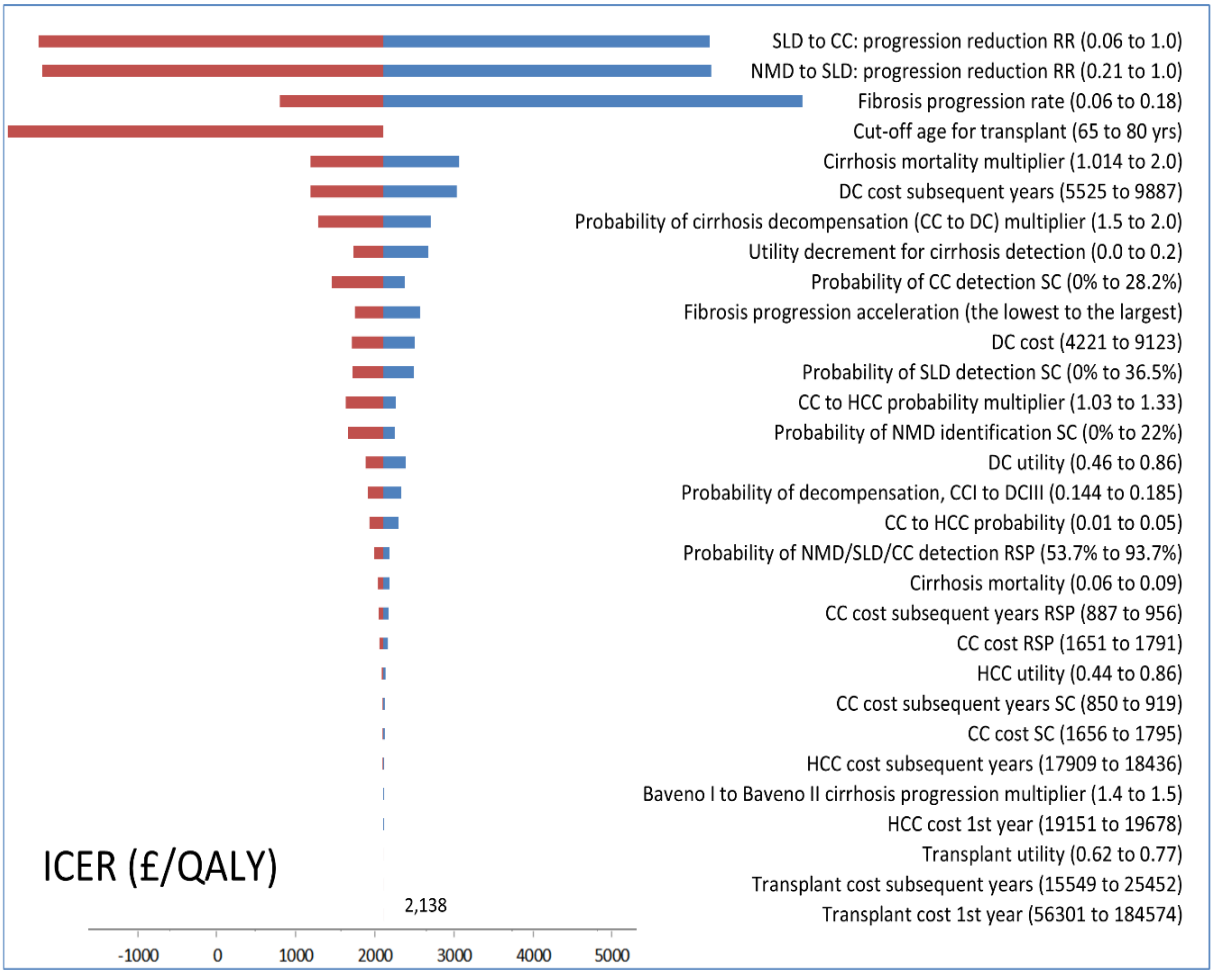
Figure 5.6 summarises results of the one way sensitivity analysis (OSAs). The two parameters with the highest impact on the ICER were:

(i) Altering the rate of fibrosis progression resulted in an ICER of £928 to £7,032 per QALY

(ii) Altering the effect of treatment on the rate of progression between NMD to SLD, and SLD to CC from the largest to no reduction (Table 5.4) resulted in an ICER ranging from -£1,895 to £5,969 per QALY gained.

See Appendix 7.8 for the results of all OSAs conducted.

Figure 5.6: Tornado diagram, NAFLD model



5.5.3 Multiway sensitivity analyses

When identification and treatment of early stage liver disease is assumed to have no effect on the rate of fibrosis progression in chronic liver disease the risk stratification pathway costs approximately £2,000 more over a life-time horizon compared with standard care due to the increased diagnostic costs over subsequent years (Table 5.15, scenario 1). When it was assumed that there was no effect of interventions used to treat patients diagnosed to have significant liver disease (SLD+), the ICER increased to £18,130/QALY (Table 5.15, scenario 2b). When it was assumed that there was no effect of intervention used to treat patients diagnosed with CC, the ICER increased to £7,669/QALY. (Table 5.15, scenario 3b).

Table 5.15: Multi-way sensitivity analyses, NAFLD model

	Cost (in £)	Incremental cost (£) RSP vs. SC	QALY	Incremental. QALY RSP vs. SC	ICER (£/QALY)
Multi-way sensitivity analysis: scenario 1^					
RSP	10,849	1,936	8.36	0	n.a.
SC	8,913		8.36		
Multi-way sensitivity analysis: scenario 2a^					
RSP	10,913	1,715	8.31	0.16	10,634
SC	9,197		8.15		
Multi-way sensitivity analysis: scenario 2b^					
RSP	10,913	1,715	8.23	0.09	18,130
SC	9,197		8.14		
Multi-way sensitivity analysis: scenario 3a^					
RSP	8,953	708	8.59	0.14	5,106
SC	8,245		8.45		
Multi-way sensitivity analysis: scenario 3b^					
RSP	8,953	708	8.53	0.09	7,669
SC	8,245		8.44		

^Assumptions on NAFLD progression:

(1) No effect of interventions on the progression of chronic liver disease (SLD+/ CC+)

(2) No effect of interventions for patients diagnosed to have significant liver disease (SLD+) whilst the base-case effect of interventions for patients diagnosed with cirrhosis remains unchanged.

(3) No effect of interventions for patients diagnosed with cirrhosis (CC+) whilst the base-case effect of interventions for patients diagnosed with significant liver disease remains unchanged.

Assumptions on utility decrement for diagnosing cirrhosis:

(a) No utility decrement

(b) Utility decrement (as in base case)

5.6 Results: Cost effectiveness of the risk stratification pathway versus standard care in ALD

5.6.1 Base case analysis

Deterministic cost-effectiveness analysis derived a mean lifetime cost per patient of £46,927 for the risk stratification pathway and £43,954 for standard care. Mean QALYs generated was 10.67 for the risk stratification pathway and 10.21 for standard care. Incremental cost was £2,973 and incremental QALY was 0.45, providing an ICER of £6,537 per extra QALY gained for the risk stratification pathway compared with standard care (Table 5.16).

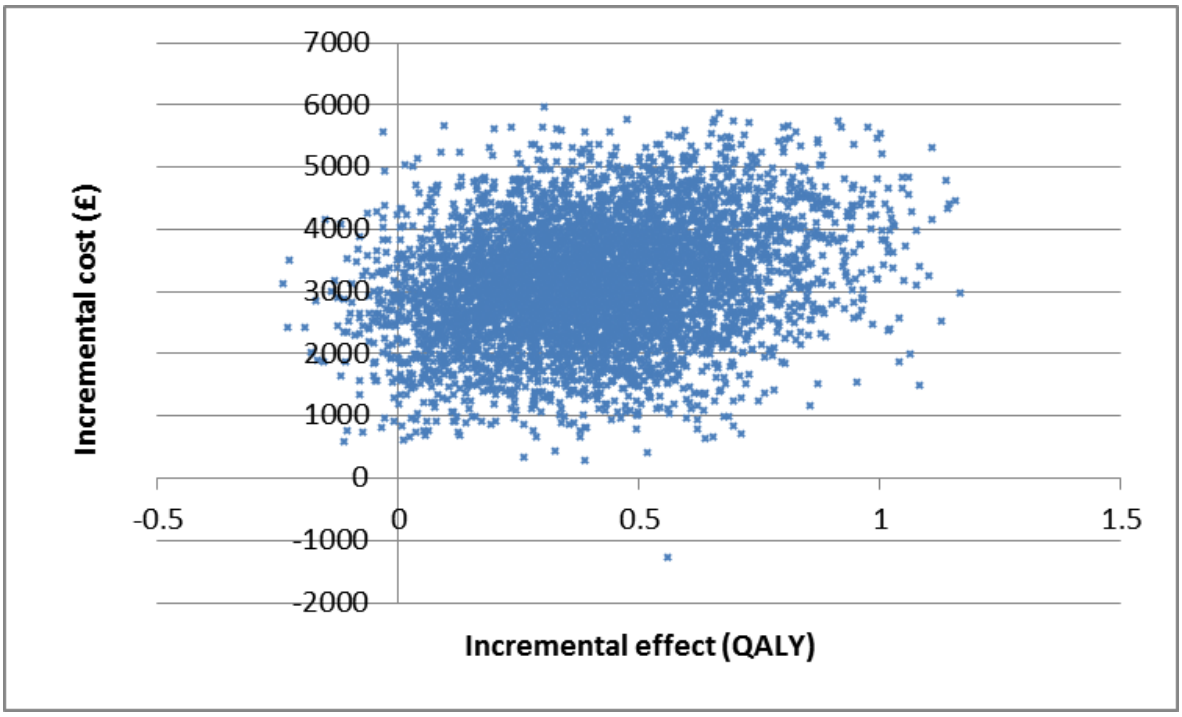
Table 5.16: Cost-effectiveness analysis of RSP vs SC: base case scenario, ALD model

Deterministic results, means					
	Cost (in £)	**Incremental cost (£) RSP vs. SC**	**QALY**	**Incremental. QALY RSP vs. SC**	**ICER (£/QALY)**
RSP	46,927	2,973	10.67	0.45	6,537
SC	43,954		10.21		
Probabilistic sensitivity analysis results, means (2.5%, 97.5% percentiles)					
RSP	42,726 (16,979; 57,037)	3,137 (1,306, 5,005)	10.19 (4.27; 16.16)	0.41 (0.00; 0.88)	7,468 (988, 51,257)
SC	39,589 (13,897; 54,461)		9.78 (4.30;15.34)		

* RSP dominated by SC (NW quadrant): 2.4%; SC dominated by RSP (SE quadrant): 0.2%; NE quadrant: 97.6%; SW quadrant: 0%.

In the probabilistic cost-effectiveness analysis, mean lifetime cost per patient (2.5% and 97.5% percentiles) were £42,726 (£16,979; £57,037) and £39,589 (£13,897; £54,461) for the risk stratification pathway and standard care respectively. Mean QALYs generated per patient (2.5% and 97.5% percentiles) were 10.91 (4.27; 16.16) for the risk stratification pathway and 9.78 (4.30; 15.34) for standard care. Incremental cost and QALYs were £3,137 (£1,306; £5,005) and 0.41 (0.00; 0.88), respectively. The ICER (2.5%, 97.5% percentiles) was £7,468 (£988; £51,257). There was an 87.5% probability that the risk stratification pathway was cost-effective at the UK willingness-to-pay threshold of £20,000/QALY (Table 5.16 and Figure 5.7).

Figure 5.7: Probabilistic sensitivity analysis: cost-effectiveness plane, ALD model



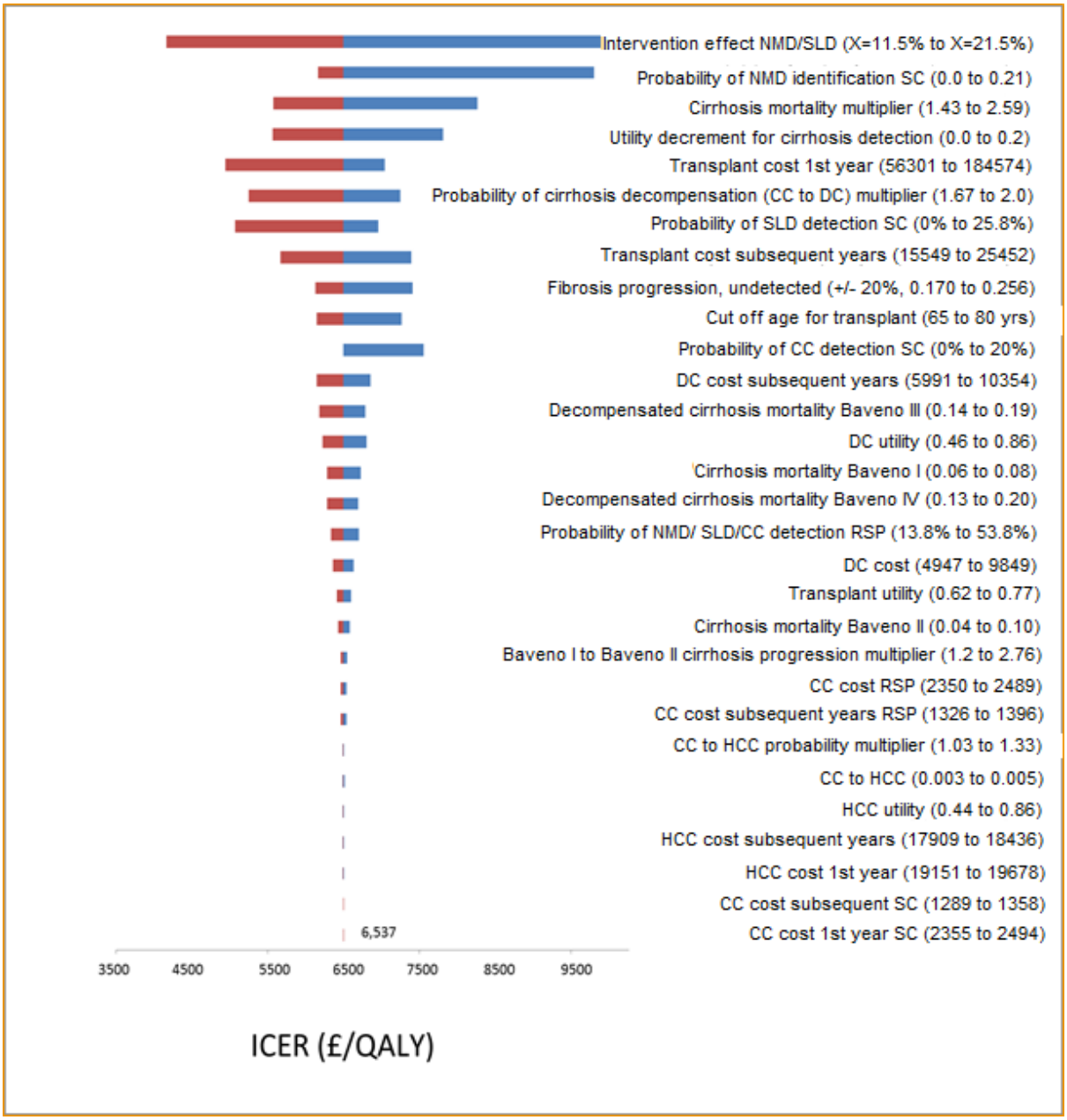
The horizontal axis represents the difference in effect between the RSP and standard care. The vertical axis represents the difference in cost. This divides the plane into four quadrants. In the North West (NW) quadrant the RSP is more costly and less effective i.e. the RSP is dominated by SC. In the South East (SE) quadrant the pathway is less costly and more effective i.e. SC is dominated by the RSP. In the North East (NE) quadrant the RSP is more

costly but more effective and choice depends on the cost effectiveness ratio one is willing to accept. In the South West (SW) quadrant the RSP is less costly but less effective than SC and would therefore not be accepted. The results within each quadrant are as follows: NW quadrant = 2.4%. SE quadrant = 0.2%. NE quadrant = 97.6%. SW quadrant = 0%.

5.6.2 One way sensitivity analyses

The parameter with the highest impact on the ICER was the effect of brief alcohol intervention on the rate of fibrosis progression (Table 5.8) resulting in an ICER ranging from £4,198 to £10,082 per QALY gained. Figure 5.8 summarises results of the one way sensitivity analysis (OSA). See Appendix 7.9 for the results of all OSAs conducted.

Figure 5.8: Tornado diagram, ALD model



5.6.3 Multiway sensitivity analyses

When diagnosis and treatment of fibrosis and cirrhosis is assumed to have no effect on the rate of disease progression and mortality (transition probabilities from NMD+, SLD+, CC+ are

the same as those from NMD-, SLD-, CC-, respectively) RSP cost approximately £6,000 more over a life-time horizon compared with SC due to the increased diagnostic costs over subsequent years (Table 5.17, scenario 1). When it was assumed that there was no effect on disease progression of diagnosing and treating patients with fibrosis (transition probabilities from NMD+ and SLD+ are the same as those from NMD- and SLD-, respectively), the ICER increased to £21,336/QALY (Table 5.17, scenario 2b). When it was assumed that there was no effect on disease progression and mortality when diagnosing or treating patients with CC+, the ICER increased to £35,332/QALY. (Table 5.17, scenario 3b).

Table 5.17: Multi-way sensitivity analyses, ALD model

	Cost (in £)	**Incremental cost (£) RSP vs. SC**	**QALY**	**Incremental. QALY RSP vs. SC**	**ICER (£/QALY)**
Multi-way sensitivity analysis: scenario 1^					
RSP	48,046	6,188	10.59	0	n.a.
SC	41,858		10.59		
Multi-way sensitivity analysis: scenario 2a^					
RSP	45,927	4,555	8.23	0.21	21,336
SC	41,372		10.90		
Multi-way sensitivity analysis: scenario 2b^					
RSP	45,927	4,555	8.31	0.31	14,595
SC	41,372		10.99		
Multi-way sensitivity analysis: scenario 3a^					
RSP	44,467	4,616	10.24	0.13	35,332
SC	41,372		10.11		
Multi-way sensitivity analysis: scenario 3b^					
RSP	44,467	4,616	10.32	0.21	21,904
SC	41,372		10.11		

^Assumptions on ALD progression:

(1) No effect of interventions on the progression of chronic liver disease (SLD+/ CC+)

(2) No effect of interventions for patients diagnosed to have significant liver disease (SLD+) whilst the base-case effect of interventions for patients diagnosed with cirrhosis remains unchanged.

(3) No effect of interventions for patients diagnosed with cirrhosis (CC+) whilst the base-case effect of interventions for patients diagnosed with significant liver disease remains unchanged.

Assumptions on utility decrement for diagnosing cirrhosis:

(a) No utility decrement

(b) Utility decrement (as in base case)

5.7 Discussion

5.7.1 Key findings

This study showed that implementation of a risk stratification pathway in the community is likely to be cost-effective according to UK cost-per-QALY thresholds, even in the presence of significant uncertainty around estimates. In the NAFLD model, the increase in cost and QALY associated with the risk stratification pathway compared with standard care was £512 and 0.24 respectively, with an ICER of £2138 per extra QALY gained. The probabilistic sensitivity analysis suggested an 85% probability of the risk stratification pathway being considered cost-effective at the UK willingness-to-pay threshold of £20,000. In the ALD model, the increase in cost and QALY associated with the risk stratification pathway compared with standard care was £2,973 and 0.45 respectively, with an ICER of £6537 per extra QALY gained. The probabilistic sensitivity analysis suggested an 88% probability of the risk stratification pathway being considered cost-effective.

5.7.2 Strengths of analysis

This is the first economic evaluation of a risk stratification pathway which targets patients in a community setting for developing NAFLD and/or ALD. Previous cost-effectiveness analyses have used a simulated cohort of patients already referred to hospital following repeated liver enzyme abnormalities, specifically a raised ALT [242, 243]. Furthermore previous health economic evaluations which have evaluated the use of transient elastography as a risk stratification tool have predominantly only been used in the context of viral hepatitis [244, 245] with only one economic evaluation extending those findings to NAFLD [243]. This study

continues that work but implements the risk stratification pathway into a community setting, a difference compared with other strategies which only assess a patient's risk of fibrosis once they have been referred to secondary care. Targeting patients with a risk factor in a community setting will enable more patients to be stratified and removes the reliance upon LFTs which have a poor specificity [82].

Iteration of the non-invasive assessment is also incorporated into this model to identify those patients who continue to be at risk and would progress to clinically significant liver fibrosis in subsequent years. Other studies are based upon a one-time assessment which does not capture the progression of disease within the natural history of NAFLD or ALD. The model is also based upon observed patient data from a primary care population in the UK to whom the risk stratification pathway was offered [157]. In the absence of data on the true prevalence of chronic liver disease in a community population this approach provides realistic estimates for the probabilities of detecting patients at risk using the risk stratification pathway or current referral algorithms.

The results of this economic analysis have been based upon conservative assumptions; therefore our estimates of cost-effectiveness represent a pessimistic scenario in which the health and economic benefits of replacing standard care with the risk stratification pathway are likely to be underestimated. Due to the complexity of the model other wider health benefits have also not been included. Steatosis within the liver results in hyperinsulinaemia and can precede the development of diabetes, hypertension and dyslipidaemia [246]. Consequently, this has also been associated with an increased prevalence of cardiovascular disease and mortality [247]. Given that the risk stratification pathway, if implemented, could also reduce the incidence of these sequelae by identifying patients at risk and allowing the opportunity for these

complications to be screened for and treated, the true impact may be underestimated. Analysis has also been completed solely from the health care perspective and thus the societal effects of implementing the pathway e.g. reduction in crime levels and work productivity gains have also not been taken into account.

5.7.3 Limitations of analysis

Limitations of our model are primarily due to the lack of appropriate data available to populate the model. Data on fibrosis progression is limited to paired biopsy studies of secondary care patients [215, 230] which may not be reflective of the natural history of chronic liver disease in a community population. The patients included within these studies are self-selected having initially presented with symptoms or are already known to have underlying liver fibrosis and therefore are more likely to return for a repeat biopsy to determine if there has been any progression of disease. Additionally, the paired liver biopsy study used in the ALD model was completed on inpatients in which the clinical indication was most likely alcoholic hepatitis [230]. Thus, the rate of fibrosis progression may not reflect the community population used within the model who are asymptomatic and have been specifically identified due to an underlying risk factor. However, varying the rate of fibrosis progression in the one way sensitivity analysis demonstrated that both models were still cost effective. Data from the paired biopsy studies was also used to determine the distribution of patients between the stages of fibrosis. Consequently, in the model, an increased number of patients are distributed to have mild to moderate liver fibrosis thus there is a higher probability of more patients progressing to cirrhosis and end stage liver disease.

Estimates of transition probabilities for the end stages of liver disease were identified from the literature but no data could be identified for those patients with undiagnosed liver disease.

Expert opinion was utilised to approximate the effect of diagnosing cirrhosis and its complications on the transition probability. Although this employs the lowest level of evidence it was assumed to be the most suitable option in light of no other alternative. Of the data which was utilised for known cases of cirrhosis [13] the probabilities for decompensation in NAFLD were obtained from the non-alcohol group inclusive of a various aetiologies e.g. viral hepatitis, metabolic liver disease and those patients in which the aetiology was not classified. The rate of decompensation in this group may therefore not be truly reflective of a NAFLD population.

Assumptions made to model the SC pathway may also not necessarily reflect current clinical practice. It was assumed that all patients identified to have abnormal LFTs in the SC arm would be referred for further investigations in concordance with current referral pathways. However, Donnan *et al* [84] has previously demonstrated that only 27.6% of patients who were identified to have abnormal LFTs were referred to secondary care. It was assumed that all patients who underwent transient elastography within the RSP who had a raised ALT would also have presented to primary care in the SC arm. As patients who attended the RSP were actively identified and invited to attend the pathway, the probabilities of detection within the SC arm may be overestimated. Results of the sensitivity analysis demonstrate that if the probability of detection in the SC arm was 0%, implementation of the RSP generated a higher incremental QALY. However, the ICER would be similar to the base case estimate (ranging between £1773-£2382 in the NAFLD model and £6,203-£6,997 in the ALD model) due to the increase in diagnostic costs for patients with early liver disease in the RSP arm compared with patients in the SC arm who would only start to accrue costs once they had progressed to the end stages of liver disease.

An important aspect of liver disease is that the liver can regenerate, leading to regression of disease if the insult is removed or lifestyle modifications are undertaken [5]. However, the regression of liver fibrosis has not been incorporated into the model as it is unclear if results from the paired biopsy studies are demonstrating true regression or whether this is secondary to sampling error [248]. Consequently an accurate transition probability could not be estimated and therefore the concept of regression was removed from the model.

The effectiveness of different pharmacological therapies in the treatment of liver fibrosis in NAFLD continues to be investigated with no individual treatment currently licensed for this specific indication. A meta-analysis of various pharmacological treatments for NAFLD [216, 249] demonstrated that the majority of studies were small and with no trial lasting more than two years the long term efficacy is still yet to be determined. Telmisartan was the only treatment within the meta-analysis which was shown to improve fibrosis in the short term [250]. However, this analysis is based upon one trial which included only 54 randomised patients. Whether the same effect can be demonstrated in the long term and in a larger cohort is still yet to be established. Thiazolidinediones, commonly known as glitazones, were one of the most commonly investigated treatments shown to consistently have an effect on the reduction of ALT levels, steatosis, liver cell injury and inflammation [216, 217, 219]. A recent study by Cusi *et al* [251] has also demonstrated an improvement in fibrosis over a follow up period of 36 months. Thus, the use of glitazones was chosen to be incorporated into the model with supporting recommendations from the National Institute of Clinical Excellence (NICE)[183] and the American Association for the Study Liver (AASLD)[104] being published during the course of this work.

Irrespective of which treatment was chosen, all of the studies which investigated the

effectiveness of different pharmacotherapies insufficiently reported the changes in a patient's fibrosis score to be able to inform the annual probability of fibrosis progression in the model. This limitation was overcome by using an individual patient dataset from the FLIRT trial [219] in order to estimate the relative reduction in fibrosis progression. The effect of pharmacotherapy on reducing the rate of fibrosis progression is therefore estimated based on the 63 patients within this trial and it is unclear how accurately this would reflect the effect of treatment in a larger population.

In the ALD model, no studies were identified which utilised brief alcohol intervention and subsequently investigated the histological effects of implementing this treatment. To overcome this limitation the results from the SIPS trial [234] which evaluated the effectiveness of brief alcohol intervention in primary care was combined with the results from a paired biopsy study [230]. It was assumed that following treatment patients who abstained from alcohol or who drank below the recommended weekly limits would have no fibrosis progression. Further research is required to determine the accuracy of this assumption and provide more accurate estimates of the effect of abstinence on the rate of fibrosis progression.

The ALD model has also not accounted for the effect of a subset of patients who would abstain or reduce their alcohol intake without any intervention. In a cross sectional retrospective survey conducted in the USA, 12.4% of people classified with prior to past year alcohol dependence would become abstinent despite never being treated for alcohol misuse [252]. The effect on the rate of fibrosis progression would be seen in both arms of the model irrespective of whether they were incorporated within the risk stratification pathway or standard care arm. The data reported in the above study [252] was not suitable to be incorporated into the model without the need for an additional set of arbitrary assumptions,

thus instead of estimating this effect it was tested within the one way sensitivity analysis. This demonstrated that arbitrarily decreasing the fibrosis progression rate, which would take into consideration the subset of patients who would stop drinking, would still result in the RSP being cost effective with an ICER of £7,452 per QALY.

Along with the limited amount of data that could be identified to estimate transition probabilities, a limited amount of QoL data was identified for patients with NAFLD and ALD. In early stage liver disease, available QoL data is limited to patients with viral hepatitis, therefore utility scores have been used from populations known to have an underlying risk factor (e.g. type 2 diabetes) as these were thought to reflect the health states of the NAFLD/ ALD population better than utilities in viral hepatitis. Although this is likely to be a good surrogate the validity of this assumption is unclear. For end-stage liver disease, QoL data were taken from studies of hepatitis C cohorts. It was assumed that QoL would be similar despite the different aetiologies but again the validity of this assumption is unclear.

Lastly, no studies were identified from a community population to determine the true diagnostic accuracy of transient elastography in comparison to the 'gold standard' investigation of a liver biopsy, although this comparison is in itself flawed due to the multiple limitations of a biopsy e.g. sampling error, standardised grading system, inter and intra observer variability. Within the model it is assumed that transient elastography combined with the diagnostic algorithm offered in the RSP or in SC arms have 100% sensitivity and specificity. Therefore the consequences of a false positive or false negative diagnosis have not been modelled. In the absence of data this assumption was considered reasonable given that all patients diagnosed with compensated cirrhosis in the original cross sectional study of the RSP had their diagnosis based upon histological, radiological and/or endoscopic findings rather

than a reading above the transient elastography threshold alone. It can also be argued that the transient elastography thresholds used within the pathway have been selected [110, 112] with a negative predictive value of greater than 90% [139] ensuring the probability of a false negative result is reduced.

Given the many uncertainties around our estimates of cost and utility occasioned by the limitations of the data outlined above we have examined carefully the potential consequences of assuming alternative values of input parameters in a series of one-way sensitivity analyses, and demonstrated that, irrespective of uncertainties in the data, the conclusions of this economic evaluation are robust.

5.7.4 Clinical implications

Whilst the medical community continue to debate whether targeting the asymptomatic via screening or implementing case finding strategies for chronic liver disease is appropriate [187] we demonstrate that our approach is at least likely to be cost effective.

The cost effectiveness of our approach is facilitated by actively identifying patients at an earlier time point within their natural history when they are at significant risk or when they already have established but undiagnosed liver disease. Implementation of brief intervention or pharmacotherapy at this time point could enable abstinence or improve diabetic control and reduce the risk of progression. A sensitivity analysis demonstrated that the cost effectiveness of this approach was maintained even when altering our estimates of long term abstinence or the effect of pharmacotherapy. If 11.5% of the screened population reduced their alcohol intake to low risk levels compared to the estimated 16.5% in the original model the ICER would equal £10082/QALY which still remains below the UK willingness-to-pay threshold of £20,000/QALY.

The risk stratification pathway we have investigated offers an opportunity to integrate liver specific interventions within diabetes care models or substance misuse clinics in the community. This does not currently happen in a systematic fashion, both because of a lack of recognition of liver disease within certain patient populations (e.g. type 2 diabetes) and the lack hitherto of available tools to identify early liver disease outside specialist care settings. The implementation of a pathway such as ours which uses pioglitazone as the treatment of choice in the NAFLD model and brief alcohol intervention in the ALD model could have implications not only for liver related morbidity and mortality but potentially may also have a knock on effect on the wide range of acute and chronic medical diagnoses caused by these underling risk factors. This is particularly pertinent to patients identified to be at risk but with no evidence of chronic liver disease at the time of attending the pathway. These patients would be educated on the range of health harms caused by their underlying risk factor which, particularly for alcohol misuse, are not commonly recognised by the wider population. Deaths directly attributable to alcohol account for only a third of the total number in which alcohol is at least partially responsible [34]. Iteration of the non-invasive test also offers a repeated opportunity to provide education on good diabetic control, healthy eating, exercise and safe alcohol limits. From the patient perspective, there are additional benefits that are not captured by this economic model. This includes the convenience of obtaining a diagnostic test and its result in a timely manner in and at a location that is convenient to their needs.

Finding the additional resources to implement new pathways represents a challenge because the benefits are long term and yet investment will be required in the short term. However, redefining how we use current diagnostic tests, including low cost but high volume liver function tests, is a key strategy. A population-based observational cohort study of patients in Tayside Scotland identified 95,977 patients who had incidental liver function tests requested

for no obvious liver disease; only 0.5 % of this cohort were found to have liver disease after two years of follow up [78]. The BALLETS study found that 38% of abnormal community liver function tests were requested as part of routine testing in chronic disease management including diabetes, hypertension and cardiovascular disease yet in almost half of these cases no underlying liver disease was subsequently found [56]. The short term benefits from social and economic issues have also not been modelled. Estimates have suggested that alcohol related crime and social disorder costs the UK tax payer £13 billion each year whilst unemployment, sickness absence and premature deaths among people of working age can cost £7.3 billion per year [36]. It may therefore be that the cost of implementing the pathway may be obtained from savings in the use of ineffective tests and from the wider society by reduced crime rates and increased employment and work productivity.

The ability to intervene earlier in the natural history of liver disease depends upon the idea that liver fibrosis is reversible or can at least have its progression retarded by intervention [188, 251] (such assumptions are clearly not unreasonable). Should the ideas we promote here be adopted, we believe that the identification of large numbers of patients with early liver disease will greatly facilitate the development of better therapies for their condition. The sensitivity analyses for our health economic model shows that as more effective treatments emerge they will further improve the ICER and may even make the pathway cost saving.

5.7.5 Future perspectives

The economic model highlights gaps in current knowledge which need to be addressed. These include the long term clinical outcomes of liver disease identified specifically by non-invasive

markers in the community. Secondary care studies suggest excellent prognostic performance of TE [253] and replication of these results from community cohorts are awaited.

A future randomised control led trial that combines diagnostic and therapeutic intervention would be the gold standard study design. However, the difficulty in defining short term outcomes, due to the inadequacy and unethical aspects of performing liver biopsies in a community setting, is balanced against the time required for long term clinical outcomes in liver disease. Thus, this study provides valuable data during this hiatus when deaths from chronic liver disease continue to rise worldwide.

5.7.6 Conclusions

In an era of increasing morbidity and mortality secondary to chronic liver disease and a lack of effective public health strategies to reduce the underlying risk factors, case finding strategies offer an opportunity to identify those most at risk and offer timely intervention. This economic analysis demonstrates that the risk stratification pathway we are proposing is feasible and cost effective.

6 Discussion

The implementation of a risk stratification pathway to diagnose chronic liver disease continues to be debated and uncertainty remains in a number of key areas. These include, but not limited to the validity of the new non-invasive tests of liver fibrosis and how these can be used to stratify patients, the potential burden of disease that may be uncovered, the lack of effective interventions that are available and the cost implications of employing such a strategy [105, 187]. This thesis has addressed some of these unanswered questions by demonstrating i) the range of non-invasive risk stratification tools that have already been utilised within a community setting ii) the type of pathway which can be successfully implemented iii) the risk factors which could be targeted and the yield from these and iv) the cost effectiveness of such a strategy.

6.1 Principal findings

From the systematic review presented in chapter 2 the burden of undetected chronic liver disease in the community was clearly demonstrated but importantly implementation of new and validated non-invasive tests for liver fibrosis in this population consistently detected a varying amount of otherwise undiagnosed disease.

Chapter 3 explored this further by carrying on from previous work by our research group [157] which implemented a community based risk stratification pathway using transient elastography and targeted patients with known risk factors. Raised body mass index (BMI) was identified to be an independent and significant solitary risk factor comparable to the

other more recognised risk factors of chronic liver disease (hazardous alcohol use and/or type 2 diabetes).

However, a known limitation of using transient elastography is the potential of recording invalid or unreliable readings in those patients who have a raised BMI. Chapter 4 analysed the performance of both the M and XL probes and demonstrated a significant increase in the number of valid and reliable readings that were obtained whilst also demonstrating that use of the correct probe is essential to ensure the patient is risk stratified correctly.

Lastly, Chapter 5 reported the results of an economic evaluation based on our pathway and reported that this was cost effective compared to the current standard of care.

6.2 Clinical implications

6.2.1 Is there a need to alter our current diagnostic pathways for chronic liver disease?

Given the rise in lifestyle related risk factors, the increase in morbidity and mortality secondary to chronic liver disease and the fact that nearly half of patients are only diagnosed once admitted to hospital [15] there is a strong argument for hepatologists to alter their current diagnostic pathways and aim to proactively identify patients before they present with a decompensating event.

From the systematic review presented in chapter 2 the burden of undiagnosed chronic liver disease in the community was clearly demonstrated. Within studies which risk stratified an unselected population, between 0.1-1.7% had evidence of cirrhosis with the reported prevalence unsurprisingly higher (2.4-4.0%) in those with an underlying risk factor. These estimates are much higher than what has been previously reported in the literature (0.07-0.13%) [28, 163] and demonstrates the frequency of chronic liver disease which is hidden within the community population.

Perhaps of more significance is the limitations of current diagnostic tests and the continued observation that the majority of these patients identified to be at risk had normal liver enzymes, commonly termed liver function tests (LFTs). These patients would not be identified by current referral pathways which are predominantly designed to investigate abnormal liver function tests. Within three studies included within the systematic review which stratified patients with an underlying risk factor, 72.4-87.5% of patients had a normal ALT level. Similarly, 74.1% of subjects in our own pathway who had an elevated transient elastography (TE) reading had normal liver function tests. Work within this thesis has reinforced the notion that a continued reliance on liver function tests to identify patients is illogical and no longer evidence based. Education of our health care colleagues [276], particularly those based within primary care, must occur to cease the inappropriate use of these tests and in partnership develop and commission new more effective diagnostic pathways for chronic liver disease. Indeed evidence obtained from work in this thesis has already had an effect on clinical practice within the local NHS trust; an integrated primary and secondary care approach to the detection and stratification of chronic liver disease has been commissioned formally by commissioners in Nottinghamshire covering a population of 0.7 million.

6.2.2 Who should be targeted?

6.2.2.1 General population vs a risk factor approach?

Whilst the argument to change practice is convincing, which patients should be approached is less clear. Whether a universal screening programme of the general population or a targeted case finding strategy for chronic liver disease is needed continues to be debated with guidelines from the European and American Associations of Liver uncommitted to a specific strategy [104, 105].

Targeting the general population ensures that all patients with asymptomatic chronic liver disease could be identified however the additional resources and costs of implementing such a strategy are likely to be significant. Caballeria *et al* [277] recently reported the prevalence of significant liver fibrosis in the general population of Catalonia, Spain, as 5.8% using TE and a threshold of >8 kPa. Similarly, Koehler *et al [278]* identified 5.6% of the general population in Rotterdam, Netherlands to have evidence of clinically relevant fibrosis using the same TE threshold.

Our own research group has demonstrated that using TE and applying the same threshold but in a targeted case finding approach (BMI ≥27.5kg/m^2 +/- type 2 diabetes +/- hazardous alcohol use) increased the proportion of patients with significant liver disease (11.7%) (Chapter 3). The proportion was even higher (26.8%) in our previous work which targeted patients with only type 2 diabetes and/or hazardous alcohol use [157]. Thus, it suggests that targeting patients with risk factors for chronic liver disease enriches the population with

individuals with significant fibrosis. Therefore, the approach could be tailored locally according to the burden of chronic liver disease and resources made available.

6.2.2.2 Which risk factors should be included within a targeted approach?

Including hazardous alcohol use and type 2 diabetes within a targeted case finding approach is logical due to the higher yield of chronic liver disease as discussed above. Chapter 3 of this thesis also demonstrated that a raised BMI should be considered in the same light after it was demonstrated to be a significant solitary risk factor.

Whilst current European and American clinical practice guidelines [104, 105] emphasise the importance of having a high index of suspicion of NAFLD in patients with type 2 diabetes we would argue that the same importance should be afforded to patients who are obese. In England, 27% of the adult population are now reported to have a BMI ≥30 kg/m^2 with estimates that this will rise to 45% by 2030 [72, 186]. Omitting obesity as an independent risk factor from any proposed case finding strategy risks missing a large proportion of patients who already have established liver disease particularly given the increasing prevalence of this risk factor within the general population. More than a third (37%) of all of the patients with an elevated TE reading (≥8.0 kPa) in our study had a raised BMI (≥27.5 kg/m^2) as their only risk factor.

However, we still do not have a complete understanding of all the risk factors for chronic liver disease and their interaction. Whilst we have started with the most plausible an uncertainty over whether other risk factors (e.g. ischaemic heart disease, hypercholesterolaemia and smoking) should also be considered as independent variables

requires further research with a clear answer only possible after larger cohort studies have been completed.

6.2.2.3 Where risk stratification should occur?

Targeted risk stratification of patients referred to secondary care would limit the applicability of any new diagnostic pathway in identifying all patients with asymptomatic chronic liver disease. Patients referred to hospital are a pre-selected cohort who have been referred based on abnormal liver function tests which do not correlate with the underlying stage of disease or who are symptomatic and therefore more likely to have cirrhosis. Referral to secondary care is also biased by other factors including the social status of the patient and the General Practitioner's education and understanding of the patient's risk of significant liver disease.

Implementation of a risk stratification pathway into a community setting offers the opportunity to proactively stratify a larger population of patients at risk with the additional advantages to the patient of ease of access to a specialised service and a reduction in costs and time when compared to attending the hospital. However, the prevalence of disease within this population group is likely to be lower which would affect the cost effectiveness and diagnostic yield of the pathway.

This has recently been demonstrated in two similar studies which have used TE to screen patients with type 2 diabetes for their risk of chronic liver disease. Kwok *et al* [279] used a threshold of 9.6kPa and identified 17.7% of the cohort to have evidence of advanced liver fibrosis. Roulot *et al* [280] used the same threshold and only identified 7.3% of the study

cohort to have advanced fibrosis. A clear difference between the two studies was the patient populations. Whilst the patients with type 2 diabetes in the study by Roulot *et al* were attending for a check-up based within a community medical centre the cohort in the study by Kwok *et al* was a mixture of referrals from both hospital and primary care clinics who were attending screening for diabetic complications. The spectrum of type 2 diabetes within these two cohorts is likely to have been different and consequently although the same TE threshold was applied a different prevalence of advanced liver fibrosis was observed.

Additional challenges with targeting a community population include the need to transfer a number of resources into a different health care setting which comes at an economic cost; currently the majority of equipment, expertise and specialist nursing staff are based within a secondary care setting. An innovative framework which crosses both primary and secondary care and integrates current community services for our 'at risk' population (e.g. alcohol misuse/ weight management services) would need to be developed in collaboration with general practitioners.

6.2.3 Which tool should be used to stratify?

A wide range of validated non-invasive tests for liver fibrosis in a community population have consistently detected otherwise undiagnosed disease. However from the systematic review reported in chapter 2, transient elastography and Fibrotest were the only two which have been validated within a community healthcare setting and compared against histological findings.

A growing evidence base is emerging for the use of transient elastography as an effective tool [112, 157, 278-280] and now coupled with the availability of a portable device which includes both the M and XL probes, we have demonstrated the feasibility and success of using it within a community based risk stratification pathway for chronic liver disease (Chapter 3). However, to be effective it needs to be applied correctly and in chapter 4 we have highlighted the importance of applying this tool accurately, specifically in an obese population.

However, other non-invasive tests created from simple blood tests and physiological parameters (e.g. Fib4, NAFLD fibrosis score) have the potential advantages of being cheaper and easier to perform in a community setting without the need for specialist training or expensive equipment as is the case with transient elastography. Thus further trials are ideally required to compare the performance of all proposed risk stratification tools in the appropriate population against the gold standard of clinical outcomes before being used within routine clinical practice.

During the course of completing this thesis several guidelines from national bodies have recommended different non-invasive tests to diagnose patients with advanced liver fibrosis. The National Institute of Clinical Excellence (NICE) has recommended the use of the Enhanced Liver fibrosis score (ELF) by primary care physicians to diagnose advanced liver fibrosis in patients with NAFLD [183]. This recommendation remains controversial as it is based upon one study of a paediatric population in a tertiary health care setting [281]. Only recently has this test been validated within primary care, however the patient population were hazardous alcohol users and therefore not at risk of NAFLD [185] and hence this diagnostic test has still not been validated within the disease specific population and setting in which the guidelines recommend its application.

Similarly, recent guidelines on the management of abnormal liver function tests from the British Society of Gastroenterology (BSG) recommend using Fib4 (combination of age, ALT, AST and platelet count) or NAFLD fibrosis score (combination of age, hyperglycaemia, body mass index, platelet count, albumin, and AST:ALT ratio) to risk stratify adults with NAFLD to determine whether they have advanced fibrosis [83]. However, the majority of evidence for these non-invasive tests is still derived from secondary care populations. Consequently application of these tests within a primary care population who have a lower prevalence of disease, as previously discussed, may lead to a variation in the performance of the test known as the spectrum effect [141, 142]. A test developed and validated within a population who have a higher prevalence of disease will likely have a lower sensitivity and higher specificity when applied in a population at lower risk [142].

Hence, the specific diagnostic test to use is still yet to be firmly established and caution is required to ensure that recent recommendations are not embedded into clinical practice until the appropriate evidence base is obtained. Utilisation without validation in the health care setting and population to which it is to be applied could lead to patients being risk stratified incorrectly resulting in a patient's disease still being missed or invasive investigations being undertaken unnecessarily.

6.2.4 Would changing our approach be cost effective?

In a time of limited resources and a financially deprived health service there is resistance to change practice unless it can be demonstrated to be cost effective and improve patient outcome. The economic evaluation of our own proposed risk stratification pathway for chronic liver disease which targeted patients with type 2 diabetes or hazardous alcohol use

was identified to be cost effective compared to current standard of care (Chapter 5). However, the main uncertainties within the economic model occurred from still not having a full understanding of the natural history of chronic liver disease or the effect of treatments on slowing or stopping the progression of disease. The current lack of sensitive non-invasive biomarkers for steatohepatitis and/or liver fibrosis to detect small changes in the underlying histopathology continues to limit our understanding of the natural progression of chronic liver disease and the effect of any new treatments which are trialled. A reliance on findings from a liver biopsy to demonstrate effectiveness is a significant limitation with uncertainty as to whether the findings that are reported are a consequence of true regression or simply a sampling error. Ideally prospective cohort studies which risk stratify patients using non-invasive tests for liver fibrosis and follow up for long term outcomes would be useful adjuncts to the current evidence but are limited by the protracted natural history of the disease which would result in clinical end points not being observed for 10-20 years.

Given the necessity for a change in practice to occur in a timelier manner evidence of behavioural change or improvement in other associated disease parameters (e.g. HbA1c in type 2 diabetics) in the short term may assist in building a body of evidence to aid translation of a new risk stratification pathway into clinical practice. Improving the network of services across primary and secondary care, which at times is lacking, and/or implementing alongside established national initiatives could be one way to instigate change and enable the pathway to be more readily adopted.

Using the mantra of 'every contact counts' [282] stratifying patients at risk of liver disease will also create an opportunity to identify patients who should also be assessed for other health complications (e.g. hypertension, hypercholesterolaemia and type 2 diabetes) and

those who should be referred to other services to initiate behavioural change e.g. alcohol misuse services [283]. The NHS Diabetes Prevention Programme (NHS DPP) has been designed to deliver behavioural interventions using tailored personalised help to reduce the risk of type 2 diabetes [284]. As eligible participants are those who have an elevated risk of developing type 2 diabetes this could easily link in and run alongside our proposed pathway.

Similarly, patients with a BMI≥30 kg/m^2 identified through the pathway could be referred for weight loss management with the possible consideration of bariatric surgery as appropriate [285]. Bariatric surgery in itself has been demonstrated to be cost effective and has been shown to improve all histological parameters of NAFLD [286, 287] which can be undiagnosed in this patient group [288]. Despite the large volume of people that would be at risk the expense of implementing the pathway and targeting those who have obesity as a risk factor could be offset by the costs of avoiding associated complications (e.g. liver disease, type 2 diabetes). Our economic model did not analyse this scenario but given the current obesity epidemic it would be clinically useful to ascertain.

6.3 Future work

Whilst implementation of a risk stratification pathway is feasible and uncovers a burden of disease which is already present in our primary care population, many unanswered questions still exist about the most effective method as discussed above. However, following on from the work undertaken in this thesis there are two avenues of research I would want to further explore.

Firstly, early identification of liver disease is only of benefit if effective interventions can be implemented to reduce the progression of disease. Whilst a risk stratification pathway gives clinicians the opportunity to identify those with liver disease it remains unknown whether this process ultimately instigates a change in the patient's behaviour which is causing them to be at risk (e.g. a reduction in their hazardous alcohol use or their BMI). This is of particular significance to those who do not yet have evidence of chronic liver disease but are highlighted to be at risk and may otherwise continue with their adverse lifestyle behaviour. Additional exploration of whether the risk stratification process in itself effectively promotes behavioural change or whether the delivery of different types of brief intervention alongside the pathway would be more effective in changing patients' behaviour requires further research. A cluster randomised control trial to study the effectiveness of different strategies would be a pragmatic way to explore this.

Secondly, we have ultimately still not answered the 'so what?' question. We have demonstrated that there is an undiagnosed burden of chronic liver disease in the community and that we now have the tools to identify these patients but in doing so are we able to make any difference to the course of the patient's disease or their prognosis. Alternatively we may in fact be doing harm by diagnosing an asymptomatic chronic disease which may not cause the patient any complications within their lifetime. Long term follow up of patients risk stratified by the proposed pathway in comparison to a cohort of at risk patients in whom the pathway was not offered, would determine whether implementing such a strategy has any effect on reducing long term clinical outcomes and overall mortality. Observation over a prolonged period of time will also enable a greater understanding of the natural history of the disease and who should be specifically targeted to obtain the greatest benefit [289].

6.4 Conclusion

This thesis has reinforced the need to change our current clinical practice and added further knowledge to the field about how and who should be targeted within a risk stratification pathway for chronic liver disease. Indeed evidence generated from this thesis has already contributed to a change in clinical practice within the local NHS trust. Along with hazardous alcohol use and type 2 diabetes, a raised BMI is a significant independent risk factor and should be considered within any targeted case finding strategy that is proposed.

Implementing such an approach is likely to be cost effective to the healthcare provider but further research is required to refine the strategy and determine the effect on long term clinical outcomes to encourage and enable adoption into clinical practice.

7 Appendix

7.1 Search algorithms used within the electronic databases

Database: Ovid MEDLINE(R) <1946 to January Week 3 2015>

Search Strategy:

Results: **329 hits**

---

1 exp Liver Cirrhosis/di [Diagnosis] (7647)

2 exp Fatty Liver/di [Diagnosis] (3112)

3 exp Liver Diseases, Alcoholic/di [Diagnosis] (1367)

4 (hepatic fibrosis or Chronic liver disease* or advanced fibrosis or non alcoholic fatty liver disease* or NAFLD or NAFL or alcoholic liver disease* or ALD or liver fibrosis* or hepatic cirrhos* or liver cirrhos* or fatty liver disease* or fatty liver or advanced fibrosis).mp. (113886)

5 exp Biological Markers/ (669858)

6 exp Elasticity Imaging Techniques/ (3985)

7 exp Diagnostic Imaging/ (1816061)

8 (non invasive biomarker* or non invasive biological marker* or non invasive marker* or fibroscan or liver stiffness or transient elastography or ultrasound abdomen or ARFI or liver function test* or LFT* or fibrotest* or fib4 or Lok or FORNS or APRI or ELF or NFS or BAAT or BARD or noninvasive biomarker* or noninvasive biological marker* or noninvasive marker* or elastogram* or sonoelastograph* or imaging tissue elastic or elasticity imaging technique*).mp.
(42847)

9 exp Family Practice/ or exp General Practice/ (65915)

10 exp Primary Health Care/ (84294)

11 exp Community Health Services/ (514681)

12 (gp or general practice* or family practice* or primary care or communit* or outreach).mp. (539188)

13 1 or 2 or 3 (10904)

14 5 or 6 or 7 or 8 (2473667)

15 4 and 14 (23298)

16 13 and 14 (4877)

17 9 or 10 or 11 or 12 (962504)

18 15 or 16 (23432)

19 17 and 18 (329)

Database: Embase <1980 to 2015 Week 03>

Search Strategy:

Results: **274 hits**

---

1 exp Liver Cirrhosis/di [Diagnosis] (10375)

2 exp Fatty Liver/di [Diagnosis] (4932)

3 exp Liver Diseases, Alcoholic/di [Diagnosis] (1672)

4 (hepatic fibrosis or Chronic liver disease* or advanced fibrosis or non alcoholic fatty liver disease* or NAFLD or
NAFL or alcoholic liver disease* or ALD or liver fibrosis* or hepatic cirrhos* or liver cirrhos* or fatty liver disease* or fatty liver or advanced fibrosis).mp. (172281)

5 exp Biological Markers/ (136914)

6 exp Elasticity Imaging Techniques/ (6192)

7 exp Diagnostic Imaging/ (120239)

8 (non invasive biomarker* or non invasive biological marker* or non invasive marker* or fibroscan or liver stiffness or transient elastography or ultrasound abdomen or ARFI or liver function test* or LFT* or fibrotest* or fib4 or LOk or FORNS or APRI or ELF or NFS or BAAT or BARD or noninvasive biomarker* or noninvasive biological marker* or noninvasive marker* or elastogram* or sonoelastograph* or imaging tissue elastic or elasticity imaging technique*).mp.
(55678)

9 exp Family Practice/ or exp General Practice/ (68233)

10 exp Primary Health Care/ (110827)

11 exp Community Health Services/ (99163)

12 (gp or general practice* or family practice* or primary care or communit* or outreach).mp. (663151)

13 exp chronic liver disease/di [Diagnosis] (1122)

14 exp early diagnosis/ (72202)

15 exp liver fibrosis/ (26007)

16 exp diagnosis/ (4570720)

17 exp non invasive measurement/ (13716)

18 chronic liver disease/ (12578)

19 exp liver cirrhosis/ (109545)

20 exp fatty liver/ (39198)

21 exp nonalcoholic fatty liver/ or exp alcohol liver disease/ (31283)

22 4 or 15 or 18 or 19 or 20 or 21 (185464)

23 5 or 6 or 7 or 8 or 14 or 17 (389042)

24 (22 or 1 or 2 or 3) and 23 (17179)

25 9 or 10 or 11 or 12 (722145)

26 24 and 25 (274)

Web of Science (169 hits)

Search performed 7th January 2015:

1 ((cirrhos* or (fatty liver) or (advanced fibrosis) or (non alcoholic fatty liver disease) or (hepatic fibrosis) or (liver fibrosis) or (chronic liver disease*) or NAFLD or NAFL or (alcoholic liver disease*) or ALD)) (175235)

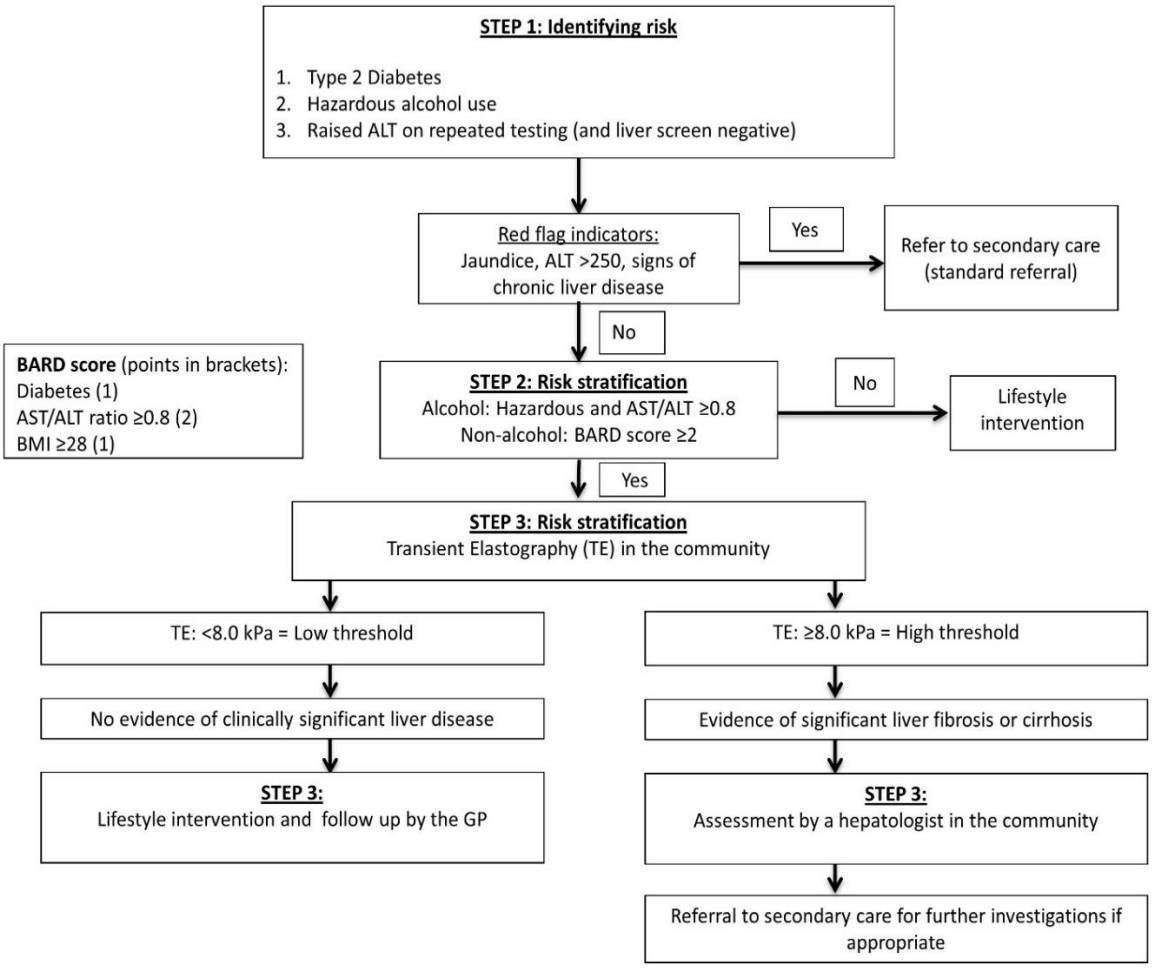
2 ((non invasive biomarker*) or (non invasive biological marker*) or (non invasive marker*) or Fibroscan or (liver stiffness) or (transient elastography) or (ultrasound abdomen) or ARFI or (live function test*) or fibrotest* or fib4 or LOK or FORNS or APRI or ELF or NFS or BAAT or BARD or elastogram* or sonoelastograph* or (imaging tissue elastic*) or (elasticity imag*)) (56346)

3 2 and 1 (8577)

4 ((general practice*) or (family practice*) or gp or gps or communit* or (primary care) or (primary healthcare) or outreach) (1,008,641)

5 4 and 3 (169)

7.2 Original risk stratification pathway used in the feasibility study by Harman *et al* [157]



7.3 Examples of Read codes to identify patients with a lifestyle related risk factor

Hazardous alcohol use:

Read Code	And Children?	Code
Hazardous Alcohol Use	Yes	XaKvA
Harmful Alcohol Use	Yes	XaKvB
Problem Drinker	Yes	Ub01R
Higher Risk Drinking	Yes	XaXje
Chronic Alcoholism	Yes	XE1YQ
Alcohol Abuse	Yes	Xa1yZ
Alcohol intake above recommended sensible limits	Yes	136K
Alcohol Dependence Syndrome	Yes	E23z

NB: Identification of patients (adults >17 years) also included searches using numerical values

-Alcohol >14 units, females only

-Alcohol >21 units, males only

-Alcohol AUDIT completed ≥8

Type 2 diabetes:

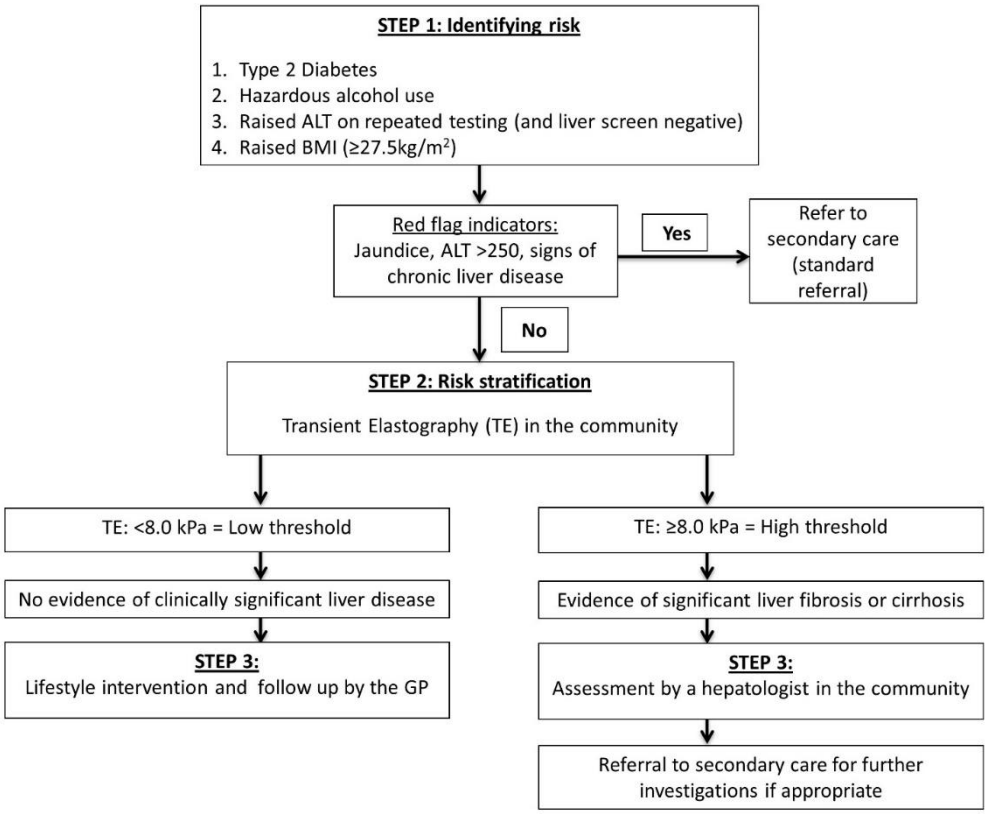
Read Code	And Children?	Code
Type 2 Diabetes	Yes	X40JS
Insulin Treated Type 2 Diabetes Mellitus	No	X40J6
Type 2 Diabetes on Insulin	No	XalfG
Type 2 Diabetes on Diet Only	No	XalfI

BMI ≥27.5 kg/m^2

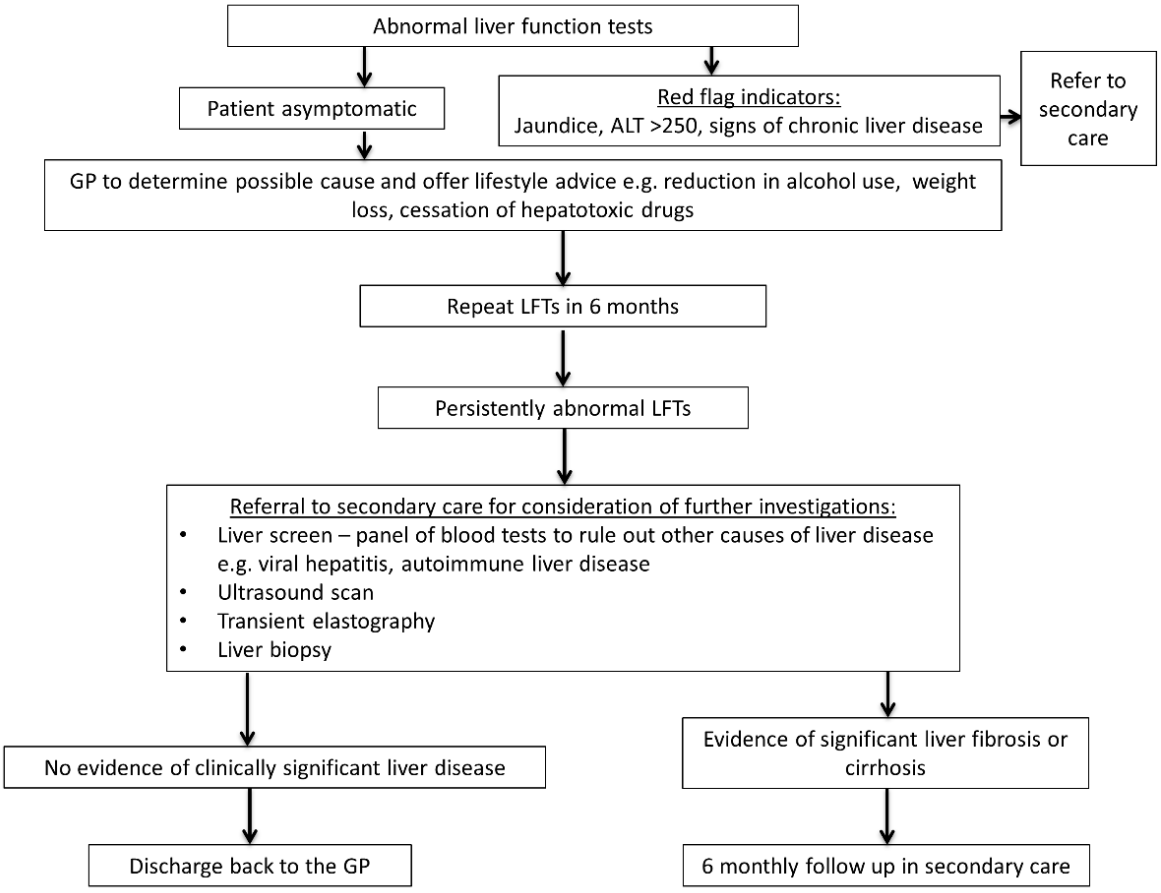
Identification of patients using numerical searches:

-All patients >17 years, with BMI>27.5 recorded in past 5 years

7.4 Risk Stratification pathway used within the study in Chapter 3



7.5 An outline of the standard care pathway



7.6 Responses obtained from the expert panel

Question related to NAFLD	Responses	Calculation of transition probability
A1. From the literature, we have identified the annual rate of patients progressing from compensated NAFLD through the stages of the Baveno classification, to decompensated NAFLD [13]. Patients with Baveno stage 1 (no ascites, no varices) progressing to Baveno stage 2 (varices, no ascites) over the course of one year = 32 patients out of 1000. How many patients per year, <u>who are not aware of their diagnosis of compensated NAFLD</u> would you expect to progress from Baveno stage 1 to Baveno stage 2? a. The number of patients progressing from Baveno stage 1 to Baveno stage 2 would stay the same. b. The number of patients progressing from Baveno stage 1 to Baveno stage 2 would increase by X=…….. patients, X < 32 c. The number of patients progressing from Baveno stage 1 to Baveno stage 2 would double.	40% increase, 16 patients	Minimal multiplier: 1.4 Maximal multiplier: 1.5(=(16+32)/32) Mean multiplier: 1.45 Annual probability of progression from CC- Baveno stage I to CC- Baveno stage II was obtained by adjusting annual probability of progression from CC+ Baveno stage I to CC+ Baveno stage II using above multiplier.
A2. From the literature we have identified that 6 out of 100 patients known to have compensated NAFLD will decompensate over the course of 1 year [221]. How many patients out of 100, <u>who are not aware of their diagnosis of compensated NAFLD</u>, would you expect to decompensate per year? a. The number of patients who would decompensate would stay the same b. The number of patients who would decompensate would increase by X=……. patients, X < 6 c. The number of patients who would decompensate would double.	3 patients, 3 patients, 6 patients, 4 patients	Minimal multiplier: 1.5(=(3+6)/6) Maximal multiplier: 2 (=(6+6)/6) Mean multiplier: 1.67 Annual probability of progression from CC- to DC was obtained by adjusting probability of progression from CC+ to DC using above multiplier.

A3. From the literature we have identified that 7 out of 100 patients, known to have compensated NAFLD will die over the course of 1 year [13]. What would you expect the all-cause mortality rate to be for patients who have compensated NAFLD but <u>who are not aware of their diagnosis?</u> a. The number of patients who would die would stay the same. b. The number of patients who would die would increase by X=……, X<7 c. The number of patients who would die would double.	2 patients, 1 patient, 7 patients, 0.1 patients (1 additional to 70/1000)	Minimal multiplier: 1.014=((0.1+7)/7) Maximal multiplier: 2 (=(7+7)/7) Mean multiplier: 1.36 Annual probability of progression from CC- to death was obtained by adjusting probability of progression from CC+ to death using above multiplier.
A4. From the literature we have identified that 30 out of 1000 patients known to have compensated NAFLD will develop a Hepatocellular carcinoma (HCC) over the course of 1 year [221]. How many patients out of 1000, <u>who are not aware of their diagnosis of compensated NAFLD</u>, would you expect to develop an HCC per year? a. The number of patients to develop an HCC would stay the same b. The number of patients to develop an HCC would increase by **X=……** patients, X<30**.** c. The number of patients to develop and HCC would double.	3 patients, 0.5 patients (5 additional to 300/1000), 10 patients, 1 patient, 1 patient,	Minimal multiplier: 1.033=((30+1)/30) Maximal multiplier: 1.33 (=(10+30)/30) Mean multiplier: 1.10 Annual probability of progression from CC- to HCC was obtained by adjusting probability of progression from CC+ to HCC using above multiplier.
Question related to ALD	**Responses**	**Calculation of transition probability**
B1. From the literature, we have identified the annual rate of patients progressing from compensated ALD through the stages of the Baveno classification, to decompensated ALD [13]. Patients with Baveno stage 1 (no ascites, no varices) progressing to Baveno stage 2 (varices, no ascites) over the course of one year = 29 patients out of 1000.	29 patients, 29 patients, 20% increase, 51 patients	Minimal multiplier: 1.2 Maximal multiplier: 2.76 (=(29+51)/29) Mean multiplier: 1.99 Annual probability of progression from CC- Baveno stage I to CC- Baveno stage II was obtained by adjusting annual probability of

How many patients per year, <u>who are not aware of their diagnosis of compensated ALD</u> would you expect to progress from Baveno stage 1 to Baveno stage 2? a. The number of patients progressing from Baveno stage 1 to Baveno stage 2 would stay the same. b. The number of patients progressing from Baveno stage 1 to Baveno stage 2 would increase by X=…… patients, X < 29 c. The number of patients progressing from Baveno stage 1 to Baveno stage 2 would double.		progression from CC+ Baveno stage I to CC+ Baveno stage II using above multiplier.
B2. From the literature we have identified that 6 out of 100 patients known to have compensated ALD will decompensate over the course of 1 year [13]. How many patients out of 100, <u>who are not aware of their diagnosis of compensated ALD</u>, would you expect to decompensate per year? a. The number of patients who would decompensate would stay the same b. The number of patients who would decompensate would increase by X=…… patients, X < 6 c. The number of patients who would decompensate would double.	4 patients, 4 patients, 6 patients	Minimal multiplier: 1.67 (=(4+6)/6) Maximal multiplier: 2 (=(6+6)/6) Mean multiplier: 1.78 Annual probability of progression from CC- to DC was obtained by adjusting probability of progression from CC+ to DC using above multiplier.
B3. From the literature we have identified that 7 out of 100 patients known to have compensated ALD will die over the course of 1 year [13]. What would you expect the all-cause mortality rate to be for patients who have compensated ALD but <u>who are not aware of their diagnosis?</u> a. The number of patients who would die would stay the same	7 patients, 4 patients, 4 patients, 3 patients, 9 patients, 3 patients	Minimal multiplier: 1.43 (=(3+7)/7) Maximal multiplier: 2.59 (=(9+7)/7) Mean multiplier: 1.71 Annual probability of progression from CC- to death was obtained by adjusting probability of progression from CC+ to death using above

b. The number of patients who would die would increase by X=……, X<7 c. The number of patients who would die would double.		multiplier.

7.7 Resource use and costs

Table 7.1: Summary of unit costs (£) across healthcare sector

Type	Resource use	Diagnosis	Unit cost (£)	Notes	Source
Primary care	GP clinic visit		46	Based on patient contact of 11.7 minutes	[213]
Secondary care	Nurse telephone consultation		8.40	Based on consultation length of 6 mins, band 5 NHS staff earnings estimate for qualified nurse	[213]
	emergency admission	Liver cirrhosis	1685.99	Based on elective admission, HRG GC17K	NHS reference costs 2013/14 [212]
	emergency admission	Ascites	1484.31	Based on elective admission, HRG FZ91M	[212]
	emergency admission	Oesophageal varices with bleeding	1317.1	Based on elective admission, HRG FZ38P	[212]
	emergency admission	HCC	1842.42	Based on elective admission, HRG GC12K	[212]
	emergency admission	Encephalopathy	2379.99	Based on non-elective admission, HRG AA22G	[212]
	outpatient visit	Liver fibrosis, cirrhosis, ascites,	217.30	Based on consultant-led	[212]

		varices or HCC – first visit		outpatient visit, TFC 306	
	outpatient visit	Liver fibrosis, cirrhosis, ascites, varices or HCC – follow-up visit	175.72	Based on consultant-led outpatient visit, TFC 306	[212]
	Planned admission	Ascites	1070.26	Based on elective admission, HRG FZ91M	[212]
	Planned admission	Oesophageal varices with bleeding	901.32	Based on elective admission, HRG FZ38P	[212]
	Planned admission	Liver cirrhosis	1061.54	Based on elective admission, HRG GC17K	[212]
	Planned admission	HCC resection	5362.01	Based on elective admission, HRG GA06D	[212]
	Planned admission	HCC follow-up	1535.32	Based on elective admission, HRG GC12K	[212]
	Transplant	First year cost	89282	Based on Longworth *et al* - cost of first 12 months, inflated to 2014 prices	[254]
	Transplant	Subsequent years cost	17077	Based on Ouwens *et al* - cost in subsequent years, converted to GBP and inflated to 2014 prices	[255]
	Day case	Day case chemoembolisation (TACE)	639.53	Based on day case cost, HRG GC12F	[212]

	Day case	HCC follow-up	359.98	Based on day case, HRG GC12K	[212]
	Day case	Ascites	400.15	Based on ascites, HRG FZ91M	[212]
	TIPS stent	Variceal bleed	3930	Based on local cost	Harman *et al* - Economic modelling of early TIPS insertion for acute variceal haemorrhage [256]
	OGD (lower estimate)		276.93	Based on outpatient visit, HRG FZ60Z	[212]
	OGD (upper estimate)		416	Local cost estimate	Harman *et al* - Economic modelling of early TIPS insertion for acute variceal haemorrhage [256]
	Fibroscan		37.30	York HE Consortium: An Economic Evaluation of Ultrasound Elastography in the Diagnosis of Liver Fibrosis [257]	[257]
	Hep B/C serology		30	Local cost estimate	Cost of HCV and HBV combined serology quoted by Queens Medical Centre virology department
	liver biopsy		546.02	Based on day cost procedure,	[212]

				HRG CZ36Y, inflated to 2014	
	Liver function test		4.52	[258] ,average across 3 sites	[258]
	Ultrasound		49.35	Based on outpatient visit, HRG RA23Z	[212]
	alpha fetoprotein		4.52		[259]
	Autoimmune liver screen		13	Wright et al (2006), average across 3 sites	[258]
	Alcohol referral services if ALD		778.66	Psychological community-based programme: £741.67 (NICE (2011) - Alcohol-use disorders, inflated to 2014)	[260]
	Dietician appointment if NAFLD		80	Dietician outpatient visit	[212]
	Hospital transport		231	Based on NHS ref cost: ambulance service code ASS02	[212]

Table 7.2: Breakdown of resource use and cost across model states in RSP: first year

State	Type	Service	Units	Min cost (£)	Max cost (£)	Source
NMD	Tests	Fibroscan	1	37.31	37.31	[151, 157]
	Primary care	GP appointment	1	46.00	46.00	[157]
		Dietician appointment if NAFLD	1	80.00	80.00	[261]
		Alcohol referral services if ALD	1	778.66	778.66	[210, 260]
	Medications	NAFLD Glitazone		19.44	19.44	[261]
Annual cost per patient for NMD state		***NAFLD***		***182.75***	***182.75***	
		ALD		***861.97***	***861.97***	
SLD	Tests	Liver function test	1	4.52	4.52	[262]
		Fibroscan	1	37.31	37.31	[151, 157]
		Hep B/C serology	1	30.00	30.00	[262]
		Ultrasound	1	49.35	49.35	[262]
		Liver biopsy	1	546.02	546.02	[263]
		Autoimmune liver screen	1	13.00	13.00	[262]
	Primary care	GP appointment	1	46.00	46.00	[262]
	Secondary care	Consultant outpatient visit	2	393.02	393.02	[262]
	Other services	Dietician appointment if NAFLD	1	80.00	80.00	[261]
		Alcohol referral services if ALD	1	778.66	778.66	[210, 260]
	Medications ‡	NAFLD		19.44	19.44	[261]
		ALD		188.63	188.63	[210]
Annual cost per patient for SLD state		***NAFLD***		***1218.65***	***1218.65***	
		ALD		***2086.50***	***2086.50***	
CC	Tests	OGD††	1	276.93	416	[264]

		Fibroscan	1	37.31	37.31	[151, 157]
		LFT	1	4.52	4.52	[262]
		Hep B/C serology	1	30.00	30.00	[262]
		Liver biopsy	1	546.02	546.02	[263]
		Ultrasound for HCC	2	98.70	98.70	[265]
		Alpha fetoprotein	2	9.04	9.04	[265]
		Autoimmune liver screen	1	13.00	13.00	[262]
	Primary care	GP appointment	1	46.00	46.00	[262]
	Secondary care	Outpatient visits	2	393.02	393.02	[262]
	Other services	Dietician appointment if NAFLD	1	80.00	80.00	[261]
		Alcohol referral services if ALD	1	778.66	778.66	[210, 260]
	Medications ‡		116.92	116.92	[210, 261, 264, 266]	
Annual cost per patient for CC state	***NAFLD***		***1651.46***	***1790.53***		
	ALD		***2350.12***	***2489.19***		
DC	Tests	OGD††	1	276.93	416	[264]
		Additional OGD for variceal bleed††	4	1107.72	1664	[264]
		Ultrasound	2	98.70	98.70	[265]
		Alpha fetoprotein	2	9.04	9.04	[265]
	Primary care	GP appointments	4	184.00	184.00	a
	Secondary care	Emergency admission if ascites	1-3	1484.31	4452.93	[267],a
		Emergency admission of variceal bleed	1-3	1317.10	3951.30	[264],a
		Emergency admission - encephalopathy	1-3	2379.99	7139.97	[268],a

		Planned admission, ascites	0-1	0	1070.26	[267, 269]
		Planned admission, variceal bleed	0-1	0	901.32	[269], a
		Outpatient visits, ascites variceal bleeds or encephalopathy	3-6	568.74	1095.90	[269], a
		TIPS stent – in 13% of patients with variceal bleed	1	3930	3930	[256, 264]
	Other services	Dietician appointment if NAFLD	1	80.00	80.00	[261]
		Alcohol referral services if ALD	1	778.66	778.66	[210, 260]
	Medications ‡	NAFLD ascites		115.05	115.05	[267]
		NAFLD variceal bleeding		20.09	20.09	[264]
		NAFLD encephalopathy		3508.67	3508.67	[270]
		ALD ascites		142.45	142.45	[210, 267]
		ALD variceal bleeding		47.48	47.48	[210, 264]
		ALD encephalopathy		3536.06	3536.06	[210, 270]
	Primary care	GP appointment	1	46.00	46.00	[262]
	Secondary care	Outpatient visits	2	393.02	393.02	[262]
	Other services	Dietician appointment if NAFLD	1	80.00	80.00	[261]
		Alcohol referral services if ALD	1	778.66	778.66	[210, 260]
	Medications ‡		116.92	116.92	[210, 261, 264, 266]	
Annual cost per patient	***NAFLD***		***1651.46***	***1790.53***		
	ALD		***2350.12***	***2489.19***		

for CC state						
DC	Tests	OGD††	1	276.93	416	[264]
		Additional OGD for variceal bleed††	4	1107.72	1664	[264]
		Ultrasound	2	98.70	98.70	[265]
		Alpha fetoprotein	2	9.04	9.04	[265]
	Primary care	GP appointments	4	184.00	184.00	a
	Secondary care	Emergency admission if ascites	1-3	1484.31	4452.93	[267] ,a
		Emergency admission of variceal bleed	1-3	1317.10	3951.30	[264] ,a
		Emergency admission - encephalopathy	1-3	2379.99	7139.97	[268] ,a
		Planned admission, ascites	0-1	0	1070.26	[267, 269]
		Planned admission, variceal bleed	0-1	0	901.32	[269] , a
		Outpatient visits, ascites variceal bleeds or encephalopathy	3-6	568.74	1095.90	[269] , a
		TIPS stent – in 13% of patients with variceal bleed	1	3930	3930	[256, 264]
	Other services	Dietician appointment if NAFLD	1	80.00	80.00	[261]
		Alcohol referral services if ALD	1	778.66	778.66	[210, 260]
	Medications ‡	NAFLD ascites		115.05	115.05	[267]
		NAFLD variceal bleeding		20.09	20.09	[264]
		NAFLD encephalopathy		3508.67	3508.67	[270]
		ALD ascites		142.45	142.45	[210, 267]
		ALD variceal bleeding		47.48	47.48	[210, 264]
		ALD encephalopathy		3536.06	3536.06	[210, 270]

Annual cost per patient for DC state*	***NAFLD***		***4221.30***	***9122.52***		
	ALD		***4947.36***	***9848.58***		
HCC	Secondary care	Nurse telephone consultations	3	25.20	25.20	a
		Hospital admission HCC resection	1	5362.01	5362.01	[265, 269, 271]
		Hospital admission – follow-up	1	1535.32	1535.32	[269], a
		Day case chemoembolisation (TACE) or radiofrequency ablation (RFA)	1	639.53	639.53	[265, 269, 271]
		Day case follow-up	1	359.98	359.98	[269], a
		Outpatient visits	4-7	744.46	1271.62	[269], a
		Hospital admission - tumour recurrence (probability 17.1%)	1	916.90	916.90	[272]
	Medications	Sorafenib		38879.17	38879.17	[265]
Annual cost per patient for HCC state				***19150.55***	***19677.76***	
Transplant	Secondary care	first year cost based on Longworth et al, subtracting cost for 2nd year based on Ouwens et al	1	89282.20 (Range 56300.60, 184574.29)†	[254, 255]	
Annual cost per patient for Transpl				***89282.20 (Range 56300.60,***		

ant state				***184574. 29)***		

a: expert panel (Dr Neil Guha, Prof Guru Aithal, Dr Martin James, Dr Stephen Ryder, Dr Toby Delahooke, Dr Emilie Wilkes, Dr Nick Taylor).

* Based on d'Amico et al [273]: ascites 51.6%, bleeding 22.8%, encephalopathy 25.5%.

** Based on proportion of patients in each treatment based on local audit data - surgical resection 17.7%; RFA 6.9%; TACE 32.7%; sorafenib 42.7% [274].

† Range of estimates derived from studies of the cost of the transplant and follow-up care in first year.

‡ For breakdown of medications used and cost, refer to Table 7.6.

†† Interval based on cost of OGD: lower estimate £277 based on NHS reference costs, HRG-4 code FZ60Z; upper estimate based on local cost found in Harman et al [256] of £416.

Table 7.3: Breakdown of resource use and cost (£) across model states in model, RSP: subsequent years

State	Type	Service	Units	Min cost	Max cost	Source
NMD	Tests	Fibroscan (every 3 years)	0.333	12.43	12.43	[193]
	Primary care	GP appointment	1	46.00	46.00	a
		Alcohol referral services IF ALD - 2/3 chance required in subsequent years	1	519.11	519.11	[210, 260]
	Medications	NAFLD Glitazone		19.44	19.44	[261, 266]
Annual cost for NMD state		***NAFLD***		***157.87***	***157.87***	
		ALD		***577.54***	***577.54***	
SLD	Tests	Liver function test	1	4.52	4.52	a
		Fibroscan	1	37.31	37.31	a, [193]
	Primary care	GP appointment	1	46.00	46.00	a
	Secondary care	Consultant outpatient visits	1	175.72	175.72	a
	Other services	Dietician appointment	1	80.00	80.00	[261]
		Alcohol referral services IF ALD - 2/3 chance required in subsequent years	1	519.11	519.11	[210, 260]
	Medications‡	NAFLD		19.44	19.44	[261, 266]
		ALD		188.63	188.63	[210]
Annual cost for SLD state		***NAFLD***		***362.99***	***362.99***	
		ALD		***971.28***	***971.28***	
CC	Tests	OGD††	0.5	138.47	208.00	[264]
		Fibroscan	1	37.31	37.31	[193], a
		LFT	2	9.04	9.04	a

		Ultrasound for HCC	2	98.70	98.70	[265], a
		Alpha fetoprotein	2	9.04	9.04	[265]
	Primary care	GP appointment	1	46.00	46.00	a
	Secondary care	Outpatient visits	2	351.44	351.44	a
	Other services	Dietician appointment	1	80.00	80.00	[261]
		Alcohol referral services IF ALD - 2/3 chance required in subsequent years	1	519.11	519.11	[210, 260]
	Medications‡			116.92	116.92	[260, 264]
Annual cost for CC state		***NAFLD***		***886.92***	***956.45***	
		ALD		***1326.03***	***1395.56***	
DC	Tests	OGD††	1	276.93	416	[264]
		Additional OGD for variceal bleed††	4	1107.72	1664	[264]
		Ultrasound	2	98.70	98.70	[265]
		Alpha fetoprotein	2	9.04	9.04	[265]
	Primary care	GP appointments	4	184.00	184.00	a
	Secondary care	Emergency admission for ascites	1-3	1484.31	4452.93	[267], a
		Emergency admission of variceal bleed	1-3	1317.10	3951.30	a, [264]
		Emergency admission, encephalopathy	1-3	2380.00	7139.97	[268], a
		Day case, ascites	6	2400.90	2400.90	[267, 269]

		planned admission, variceal bleeds	0-1	0	901.32	[269], a
		Outpatient visits, ascites or variceal bleeds	3-6	527.16	1054.32	[269], a
		TIPS stent – 13% of patients with variceal bleed	1	3930	3930	[256, 264]
	Other services	Dietician appointment	1	80.00	80.00	[261]
		Alcohol referral services IF ALD - 2/3 chance required in subsequent years	1	519.11	519.11	[210, 260]
	Medications‡	NAFLD ascites		115.05	115.05	[267]
		NAFLD variceal bleeding		20.09	20.09	[264]
		NAFLD encephalopathy		3508.67	3508.67	[270]
		ALD ascites		142.45	142.45	[210, 267]
		ALD variceal bleeding		47.48	47.48	[210, 264]
		ALD encephalopathy		3536.06	3536.06	[210, 270]
Annual cost for DC state*	***NAFLD***		5524.99	9887.17		
	ALD		5991.49	10353.67		
HCC	Secondary care	Nurse telephone consultations	3	25.20	25.20	a
		Hospital admission – follow-up	1	1535.32	1535.32	[269], a
		Day case follow-up	1	359.98	359.98	[269], a
		outpatient visits	4-7	702.88	1230.04	[269], a
		Hospital admission -	1	916.90	916.90	[272], a

		tumour recurrence (probability 17.1%)				
	Medications	Sorafenib		38879.17	38879.17	[265]
Annual cost for HCC state*			***17908.99***	***18436.21***		
Transplant	Re-transplantation	Based on Longworth et al, probability 5%	0.05	4464.11 (range 2815.03, 9228.71)†	[254]	
	OR subsequent care	Based on Ouwens at al – prob 95%	0.95	16223.33 (range 12733.94, 16223.33)†	[255]	
Annual cost for transplant state**		***20687.44 (range 15548.97-25452.04)***				

a: expert panel (Dr Neil Guha, Prof Guru Aithal, Dr Martin James, Dr Stephen Ryder, Dr Toby Delahooke, Dr Emilie Wilkes, Dr Nick Taylor).

* Based on d'Amico et al [273]: ascites 52.4%, bleeding 18.8%, encephalopathy 28.8%.

** Based on proportion of patients in each treatment based on local audit data - surgical resection 17.7%; RFA 6.9%; TACE 32.7%; sorafenib 42.7% [274].

*** The mean cost for the transplant state in subsequent years was calculated based on probability of 5% of re-transplantation in subsequent years after the first procedure[269], in which case the cost for first year of transplant from Longworth et al [254] would be applied; in other cases (probability 95%) the follow-up year cost from Ouwens et al [255] would be applied.

† Range of estimates derived from studies of the cost of follow-up care in subsequent years.

‡ For breakdown of medications used and cost, refer to Table 7.6.

†† Interval based on cost of OGD: lower estimate £277 based on NHS reference costs, HRG-4 code FZ60Z; upper estimate based on local cost found in Harman et al [256] of £416.

Table 7.4: Breakdown of resource use and cost (£) across model states, standard care: first year

State	Type	Service	Units	Min cost	Max cost	Source
NMD	Tests	Fibroscan	1	37.31	37.31	[193, 261]
		LFT	2	9.04	9.04	[262]
		Hep B/C serology	1	30.00	30.00	[262]
		Autoimmune liver screen	1	13.00	13.00	[262]
		Ultrasound	1	49.35	49.35	[262]
		Liver biopsy	1	546.02	546.02	[263]
	Primary care	GP appointment	1	46.00	46.00	[262]
	Secondary care	Consultant outpatient visit	2	393.02	393.02	[262]
	Other services	Dietician services	1	80.00	80.00	[261]
		Alcohol referral services	1	778.66	778.66	[210, 260]
	Medications	NAFLD glitazone		19.44	19.44	a, [261]
Annual cost for NMD state		***NAFLD***		***1223.18***	***1223.18***	
		ALD		***1902.40***	***1902.40***	
SLD	Tests	Liver function test	2	9.04	9.04	[262]
		Fibroscan	1	37.31	37.31	[193]
		Hep B/C serology	1	30.00	30.00	[262]
		Ultrasound	1	49.35	49.35	[262]
		Liver biopsy	1	546.02	546.02	[263]
		Autoimmune liver screen	1	13.00	13.00	[262]
	Primary care	GP appointment	1	46.00	46.00	[262]
	Secondary care	Consultant outpatient visit	2	393.02	393.02	[262]

	Other services	Dietician appointment	1	80.00	80.00	[261]
		Alcohol referral services	1	778.66	778.66	[210, 260]
	Medications ‡	NAFLD		19.44	19.44	[261]
		ALD		188.63	188.63	[210]
Annual cost for SLD state	***NAFLD***		***1223.18***	***1223.18***		
	ALD		***2091.02***	***2091.02***		
CC	Tests	OGD	1	276.93	416	[264]
		Fibroscan	1	37.31	37.31	[193]
		LFT	2	9.04	9.04	[262]
		Hep B/C serology	1	30.00	30.00	[262]
		Liver biopsy	1	546.02	546.02	[263]
		Ultrasound for HCC	2	98.70	98.70	[265]
		Alpha fetoprotein	2	9.04	9.04	[265]
		Autoimmune liver screen	1	13.00	13.00	[262]
	Primary care	GP appointment	1	46.00	46.00	[262]
	Secondary care	Outpatient visits	2	393.02	393.02	a, [262]
	Other services	Dietician appointment	1	80.00	80.00	[261]
		Alcohol referral services	1	778.66	778.66	[210, 260]
	Medications ‡		116.92	116.92	[210, 264]	
Annual cost for CC state			***1655.98***	***1795.05***		
			2354.64	***2493.71***		
DC	Tests	OGD††	1	276.93	416	[264]
		Additional OGDs for variceal bleed††	4	1107.72	1664	[264]
		Ultrasound	2	98.70	98.70	[265]

		Alpha fetoprotein	2	9.04	9.04	[265]
	Primary care	GP appointments	4	184.00	184.00	a
	Secondary care	Emergency admission if ascites	1-3	1484.31	4452.93	a, [267]
		Emergency admission of variceal bleed	1-3	1317.10	3951.30	[264], a
		Emergency admission for encephalopathy	1-3	2379.99	7139.97	[268], a
		Planned admission, ascites	0-1	0	1070.26	[267, 269]
		Planned admission, variceal bleed	0-1	0	901.32	[269], a
		Outpatient visits, ascites or variceal bleeds	3-6	568.74	1095.90	[269], a
		TIPS stent - in 13% of patients with variceal bleed	1	3930	3930	[256, 264]
	Other services	Dietician appointment	1	80.00	80.00	[261]
		Alcohol referral services	1	778.66	778.66	[210, 260]
	Medications	NAFLD ascites		115.05	115.05	[267]
		NAFLD variceal bleeding		20.09	20.09	[264]
		NAFLD encephalopathy		3508.67	3508.67	[270]
		ALD ascites		142.45	142.45	[210, 267]
		ALD variceal bleeding		47.48	47.48	[210, 264]
		ALD encephalopathy		3536.06	3536.06	[210, 270]
Annual cost for DC state*	***NAFLD***		***4221.30***	***9122.52***		
	ALD		***4947.36***	***9848.58***		
HCC	Secondary care	Nurse telephone consultations	3	25.20	25.20	a

		Hospital admission HCC resection	1	5362.01	5362.01	[265, 269, 271]
		Hospital admission – follow-up	1	1535.32	1535.32	[269], a
		Day case chemoembolisation (TACE) or radiofrequency ablation (RFA)	1	639.53	639.53	[265, 269, 271]
		Day case follow-up	1	359.98	359.98	[269], a
		Outpatient visits	4-7	744.46	1271.62	[269], a
		Hospital admission - tumour recurrence (probability 17.1%)	1	916.90	916.90	[272], a
	Medications	Sorafenib		38879.17	38879.17	[265]
Annual cost for HCC state*			***19150.55***	***19677.76***		
Transplant	All services	First year cost: based on Longworth et al and subtracting cost for 2nd year from Ouwens et al	1	89282.20 (Range 56300.60, 184574.29)†	[254, 255]	
Annual cost for transplant state			***89282.20 (Range 56301.60, 184574.29)***			

a: expert panel (Dr Neil Guha, Prof Guru Aithal, Dr Martin James, Dr Stephen Ryder, Dr Toby Delahooke, Dr Emilie Wilkes, Dr Nick Taylor).

* Based on d'Amico et al [273]: ascites 51.6%, bleeding 22.8%, encephalopathy 25.5%.

** Based on proportion of patients in each treatment based on local audit data - surgical resection 17.7%; RFA 6.9%; TACE 32.7%; sorafenib 42.7% [274].

† Range of estimates derived from studies of the cost of the transplant and follow-up care in first year.

‡ For breakdown of medications used and cost, refer to Table 7.6.

†† Interval based on cost of OGD: lower estimate £277 based on NHS reference costs, HRG-4 code FZ60Z; upper estimate based on local cost found in Harman et al [256] of £416.

Table 7.5: Breakdown of resource use and cost (£) across model states, standard care: subsequent years

State	Type	Service	Units	Min cost	Max cost	Source
NMD	Primary care	GP visit (NAFLD)		46.00	46.00	a
	Medications	Glitazone (NAFLD)		19.44	19.44	a
Annual cost for NMD state		***NAFLD***		***65.44***	***65.44***	
		ALD		***0***	***0***	
SLD	Tests	Liver function test	2	9.04	9.04	a
		Fibroscan	1	37.31	37.31	[193]
	Primary care	GP appointment	1	46.00	46.00	a
	Secondary care	Consultant outpatient visits	1	175.72	175.72	a
	Other services	Dietician appointment	1	80.00	80.00	[261]
		Alcohol referral services IF ALD- 2/3 chance required in subsequent years	1	519.11	519.11	[210], [260]
	Medications‡	NAFLD		19.44	19.44	[261]
		ALD		188.63	188.63	[210]
Annual cost for SLD state		***NAFLD***		***367.51***	***367.51***	
		ALD		***975.81***	***975.81***	
CC	Tests	OGD††	0.5	138.47	208	[264]
		LFT	2	9.04	9.04	a
		Ultrasound for HCC	2	98.70	98.70	[265]
		Alpha fetoprotein	2	9.04	9.04	[265]
	Primary care	GP appointment	1	46.00	46.00	a
	Secondary care	Outpatient visits	2	351.44	351.44	a
	Other services	Dietician appointment	1	80.00	80.00	[261]
		Alcohol referral services IF ALD - 2/3 chance required in subsequent years	1	519.11	519.11	[210],[260]
	Medications‡			116.92	116.92	[210, 264]
	NAFLD		***849.61***	***919.14***		

Annual cost for CC state	***ALD***		***1288.72***	***1358.25***		
DC	Tests	OGD††	1	276.93	416	[264]
		Additional OGDs for variceal bleed††	4	1107.72	1664	[264]
		Ultrasound	2	98.70	98.70	[265]
		Alpha fetoprotein	2	9.04	9.04	[265]
	Primary care	GP appointments	4	184	184	a
	Secondary care	Emergency admission – ascites	1-3	1484.31	4452.93	[267]
		Emergency admission – variceal bleeding	1-3	1317.10	3951.30	[264]
		Emergency admission - encephalopathy	1-3	2379.99	7139.97	[268], a
		Day case, ascites	6	2400.9	2400.9	[267], [269]
		planned admission, variceal bleeds	0-1	0	901.32	a, [269]
		Outpatient visits, ascites or variceal bleeds	3-6	527.16	1054.32	a, [269]
		TIPS stent - in 13% of patients with variceal bleed	1	3930	3930	[264], [256]
	Other services	Dietician appointment	1	80.00	80.00	[261]
		Alcohol referral services IF ALD - 2/3 chance required in subsequent years	1	519.11	519.11	[210], [260]
		NAFLD ascites		115.05	115.05	[267]
	Medications‡	NAFLD variceal bleeding		20.09	20.09	[264]
		NAFLD encephalopathy		3508.67	3508.67	[270]
		ALD ascites		142.45	142.45	[210, 267]
		ALD variceal bleeding		47.48	47.48	[210, 264]

		ALD encephalopathy		3536.06	3536.06	[210, 270]
Annual cost for DC state*	***NAFLD***		***5524.99***	***9887.17***		
	ALD		***5991.49***	***10353.67***		
HCC	Secondary care	Nurse telephone consultations	3	25.20	25.20	a
		Hospital admission, follow-up	1	1535.32	1535.32	a, [269]
		Day case follow-up	1	359.98	359.98	
		Outpatient visits	4-7	702.88	1230.04	a, [269]
		Hospital admission - tumour recurrence (probability 17.1%)	1	916.90	916.90	[272], a
	Medications	Sorafenib		38879.17	38879.17	[265]
Annual cost for HCC state			***17908.99***	***18436.21***		
Transplant	Re-transplant OR subsequent care	Based on Longworth et al and Ouwens et al, probability 5%	0.05	4464.11 (range 2815.03, 9228.71)†	[254], [255]	
		Based on Ouwens at al – prob 95%	0.95	16223.33 (range 12733.94, 16223.33) †	[255]	
Annual cost for Transplant state***		***20687.44 (range 15548.97-25452.04)***				

a: expert panel (Dr Neil Guha, Prof Guru Aithal, Dr Martin James, Dr Stephen Ryder, Dr Toby Delahooke, Dr Emilie Wilkes, Dr Nick Taylor).

* Based on d'Amico et al [273]: ascites 52.4%, bleeding 18.8%, encephalopathy 28.8%.

** Based on proportion of patients in each treatment based on local audit data - surgical resection 17.7%; RFA 6.9%; TACE 32.7%; sorafenib 42.7% [274].

*** The mean cost for the transplant state in subsequent years was calculated based on probability of 5% of re-transplantation in subsequent years after the first procedure [269], in which case the cost for first year of transplant from Longworth et al [254] would be applied;

in other cases (probability 95%) the follow-up year cost from Ouwens et al [255] would be applied.

† Range of estimates derived from studies of the cost of the transplant and follow-up care in first year.

‡ For breakdown of medications used and cost, refer to Table 7.6.

†† Interval based on cost of OGD: lower estimate £277 based on NHS reference costs, HRG-4 code FZ60Z; upper estimate based on local cost found in Harman et al [256] of £416.

Table 7.6: Cost (£) of medications

State	Medication	Dose	Daily frequency	Unit cost (£)	Pack supply	Days supply	Yearly cost
NMD	Pioglitazone	30	1	1.49	840	28	19.44
Subtotal							19.44
SLD	Pioglitazone	30	1	1.49	840	28	19.44
	Acamprosate	666	3	28.92	111888	56	188.63
Subtotal							208.06
CC	Carvidilol	12.5	1	1.54	350	28	20.09
	Multivitamins	2	1	11.93	90	45	96.83
Subtotal							116.92
DC	Carvidilol – secondary prophylaxis for variceal bleeding	12.5	1	1.54	350	28	20.09
	Thiamine – Prevention of Wernicke-Korsakoff syndrome	100	1	1.5	2000	20	27.39
	Spironolactone – ascites	100	2	3.55	2800	14	92.62
	Furosemide – ascites	40	2	0.86	1120	14	22.44
	Rifaximin - encephalopathy	550	2	259.23	56	28	3381.56
	Lactulose - encephalopathy	20	3	2.9	500	8.333333	127.11
Subtotal	ALD ascites						142.45
	ALD variceal bleeding						47.48
	ALD encephalopathy						3536.06
	NAFLD ascites						115.05
	NAFLD variceal bleeding						20.09
	NAFLD encephalopathy						3508.67
HCC	Sorafenib	400	2	2980.47	22400	28	38879.17
Subtotal							38879.17
Transplant	Tacrolimus	2	2	111.36	100	25	1626.97
	Azathioprine	100	1	3.54	2800	28	46.18
	Prednisolone	29.23	1	1.33	140	4.7896	25.27
Subtotal first year							1698.42
Subtotal subsequent years							1626.97

7.8 Assumptions and results of one-way sensitivity analyses (NAFLD model)

Parameter (base-case value)	Minimal/ maximal / alternative value	Comment / source	Incremental cost (£)	Incremental QALY	ICER (£/QALY)
		Base case	512	0.24	2138
Costs (£)					
Cost of transplant (1st year), 89282	56301	The lowest estimate identified [275]	512	0.24	2138
	184574	The highest estimate identified [227]	512		2138
Cost of transplant (subsequent years), 20687	15549	The lowest estimated cost	512		2138
	25452	The highest estimated cost	512		2138
Cost of HCC (1st year), 19414	19151	Assumed 4 outpatient visits per year	513		2143
	19678	Assumed 7 outpatient visits per year	511		2134
Cost of HCC (subsequent years), 18172	17909	Assumed 4 outpatient visits per year	514		2148
	18436	Assumed 7 outpatient visits per year	509		2129
Cost of DC (1st year), 6672	4221	The lowest estimate	600		2507
	9123	The highest estimate	423		1770
Cost of DC (subsequent years), 7706	5525	The lowest estimate	716		2992
	9887	The highest estimate	307		1285
Cost of NMD, RSP (subsequent years), 158	153	Fibroscan test once per 5 years	490		2050
Cost of CC, RSP, 1721	1651	The lowest and the highest estimate	499		2086
	1791		524		2191
Cost of CC, RSP (subsequent years), 921	887		497		2079
	956		526		2200
Cost of CC, SC, 1725	1656		514		2150
	1795		509		2127
Cost of CC, SC (subsequent years), 884	850		515		2151
	919		508		2125
Utilities					
Transplant utility, 0.69	0.62	Lower 95%CI limit [241]	512	0.24	2138
	0.77	Upper 95% CI limit [241]		0.24	2138
HCC utility, 0.65	0.44	Lower 95%CI limit		0.24	2115
	0.86	Upper 95%CI limit		0.24	2163
DC utility, 0.66	0.46	Lower 95%CI limit		0.27	1929

	0.86	Upper 95%CI limit		0.21	2398
Utility decrement for detection of CC, 0.1	0	Arbitrary assumption		0.29	1789
	0.2	Arbitrary assumption		0.19	2658
Probabilities					
Reduction of progression from SLD to CC (relative risk, RR), 0.63	0.06	Lower limit of 95% CI	-766	0.40	-1895
	1	Assumed no effect	971	0.16	5948
Reduction of progression from NMD to SLD (relative risk, RR), 0.67	0.21	Lower limit of 95% CI	-594	0.32	-1852
	1	Assumed no effect	1126	0.19	5969
Probability of decompensation multiplier (CC- to DC)*, 1.7	1.5	Minimal and maximal multipliers based on expert panel responses	600	0.22	2686
	2.0		364	0.26	1373
Mortality from CC-multiplier, 1.4**	1.0		488	0.24	2069
	2.0		549	0.25	2246
Probability of HCC multiplier (CC- to HCC)*, 1.1**	1.0		543	0.24	2282
	1.3		413	0.24	1695
Probability CCI to CCII multiplier (undetected), 1.45	1.4		513	0.24	2144
	1.5		510	0.24	2133
Fibrosis progression rate	0.06	Lower 95%CI limit in [215]	857	0.12	7032
	0.18	Upper 95%CI limit in [215]	321	0.35	928
Acceleration of progression**, **14.8 / 9.2 / 5.7 / 3.6**	13.1 / 9.2 / 6.5 / 4.1	The lowest acceleration rate as indicated by experts	549	0.21	2561
	16.5 / 9.1 / 5.0 / 2.7	The highest acceleration rate as indicated by experts	478	0.27	1800
Probability CCI ->DCIII, 16.4%	14.4%	Lower and upper limits of 95% CIs in [13]	557	0.24	2346
	18.5%		470	0.24	1953
CCI->DCIV, 0.8%	0.4%		525	0.24	2195
	1.5%		489	0.24	2044
CCII->DCIII, 17.1%	13.8%		518	0.24	2163
	20.8%		506	0.24	2117
CCII->DCIV, 5.1%	3.3%		517	0.24	2160
	7.5%		506	0.24	2115
CCI ->death, 7.5%	6.1%		491	0.24	2072
	9.1%		533	0.24	2207
CCII->death, 6.6%	3.9%		509	0.24	2128
	10.3%		515	0.24	2152
DCIII to death, 25.1%	22.3%		413	0.23	1783
	28.1%		601	0.25	2442
DCIV to death, 20.4%	16.2%		474	0.24	2005
	25.2%		543	0.24	2247

CC1 to CCIII, 3.2%	2.3%		515	0.24	2154
	4.4%		507	0.24	2118
DCIII to DCIV, 3.2%	2.1%		517	0.24	2158
	4.6%		505	0.24	2115
Probability of detection NMD/SLD/CC RSP, 73.7%	53.7%	Arbitrary increase and decrease by 20 percentage points (0% assumed if negative percentage).	408	0.20	2032
	93.7%		586	0.27	2204
Probability of detection NMD, SC, 2.0%	0%		557	0.25	2265
	22.0%		344	0.20	1719
Probability of detection SLD, SC, 16.5%	0%		619	0.35	1773
	36.5%		443	0.18	2497
Probability of detection CC, SC, 8.2%	0%		613	0.26	2382
	28.2%		313	0.20	1530
Mortality 1st year after transplant, 16.6%	12%	Alternative input parameter [221]	512	0.24	2138
Probability CC+ to HCC, 3%	0.7%	The minimal value in [221]	561	0.24	2313
	5%	The maximal value in [221]	467	0.24	1969
Cut-off age for transition probability to transplant from both DC and HCC	65 yrs	Assumed cut-off for DC to transplant the same as for HCC	512	0.24	2138
	70 yrs	Assumed cut-off for HCC to transplant the same as for DC	512	0.24	2138
	80 yrs	Arbitrary	-495	0.22	-2254

* Expert panel. Annual probability of progression from CC- to DC was obtained by multiplying probability of progression from CC+ to DC.

** Expert panel. Annual probability of death from CC- was obtained by multiplying probability of death from CC+.

*** Expert panel. Annual probability of HCC from CC- was obtained by multiplying probability of HCC from CC+.

**** Notation: 14.8 / 9.2 / 5.7 / 3.6 reflects stage 0 to 1, stage 1 to 2, stage 2 to 3, and stage 3 to 4 mean times of progression in years, respectively.

7.9 Assumptions and results of one-way sensitivity analyses (ALD model)

Parameter (base-case value)	Minimal/ maximal / alternative value	Comment / source	Incremental cost (£)	Incremental QALY	ICER (£ /QALY)
		Base case	2973	0.45	6537
Costs (£)					
Cost of transplant (1st year), 89282	56301	The lowest estimate identified [275]	3218		7079
	184574	The highest estimate identified [227]	2261		4974
Cost of transplant (subsequent years), 20687	15549	The lowest estimated cost	3880		7434
	25452	The highest estimated cost	2596		5706
Cost of HCC (1st year), 19414	19151	Assumed 4 outpatient visits per year	2973		6538
	19678	Assumed 7 outpatient visits per year	2972		6537
Cost of HCC (subsequent years), 18172	17909	Assumed 4 outpatient visits per year	2973		6538
	18436	Assumed 7 outpatient visits per year	2972		6537
Cost of DC (1st year), 7398	4947	The lowest estimate	3035		6675
	9849	The highest estimate	2910		6400
Cost of DC (subsequent years), 8172	5991	The lowest estimate	3135		6894
	10354	The highest estimate	2810		6181
Cost of NMD, RSP (subsequent years), 578	573	Fibroscan test once per 5 years	2956	0.45	6501
Cost of CC, RSP, 2419	2350	The lowest and the	2954		6497
	2489		2991		6578
Cost of CC, RSP (subsequent years), 1361	1326		2955		6499
	1396		2990		6576
Cost of CC, SC,	2355		2973		6537

2424	2494	highest estimates	2973		6537
Cost of CC, SC (subsequent years), 1323	1289		2973		6537
	1358		2973		6537
Utilities					
Transplant utility, 0.69	0.62	Lower and upper limits of 95%CI in [241]	2973	0.46	6451
	0.77			0.45	6639
HCC utility, 0.65	0.44			0.46	6529
	0.86			0.45	6546
DC utility, 0.66	0.46			0.47	6262
	0.86			0.43	6838
Utility decrement for detection of CC, 0.1	0	Arbitrary assumption		0.53	5601
	0.2	Arbitrary assumption		0.38	7851
Probabilities					
Average fibrosis progression rate (detected), X=16.5%, 0.178*	11.5% / 0.188	Lower and upper 95% CI calculated for the percentage X% = 35 / 212 [234] and corresponding fibrosis progression rates.	3517	0.35	10082
	21.5% / 0.167		2381	0.57	4198
Probability of decompensation multiplier (CC- to DC), 1.8	1.7	Minimal and maximal multipliers based on expert panel responses	3309	0.45	7289
	2.0		2405	0.45	5284
Mortality from CC-multiplier, 1.7	1.4		2317	0.41	5606
	2.6		4643	0.56	8305
Probability of HCC multiplier (CC- to HCC), 1.1	1.0		2974	0.45	6546
	1.3		2969	0.46	6521
Probability CCI to CCII multiplier (undetected), 1.99	1.2		2994	0.45	6581
	2.8		2953	0.45	6498
Fibrosis progression rate, 0.213	0.170	Arbitrary: 20% decrease	3407	0.46	7452
	0.256	Arbitrary: 20% increase	2716	0.44	6166

CCI ->DCIII, 24.1%	21.8%	Lower and upper limits of 95% CIs in [13]	3033	0.47	6510
	26.5%		2919	0.44	6567
CCI->DCIV, 1.5%	0.9%		2988	0.46	6531
	2.3%		2953	0.45	6546
CCII->DCIII, 17.4%	13.0%		2992	0.46	6553
	22.5%		2956	0.45	6526
CCII->DCIV, 9.3%	6.0%		2987	0.46	6549
	13.5%		2959	0.45	6527
CCI ->death, 7.0%	5.7%		2887	0.46	6321
	8.5%		3062	0.45	6766
CCII->death, 6.6%	3.9%		2933	0.45	6462
	10.3%		3017	0.46	6621
DCIII to death, 16.4%	14.3%		2783	0.45	6220
	18.6%		3148	0.46	6823
DCIV to death, 16.5%	13.1%		2843	0.45	6321
	20.5%		3092	0.46	6733
CCI to CCII, 2.9%	2.1%		2978	0.46	6531
	4.0%		2965	0.45	6545
DCIII to DCIV, 7.3%	5.9%		2972	0.45	6537
	8.9%		2973	0.45	6539
Probability of detection NMD/SLD/CC RSP, 33.8%	13.8%	Arbitrary increase and decrease by 20 percentage points (0% assumed if negative percentage).	1549	0.23	6736
	53.8%		3699	0.58	6370
Probability of detection NMD, SC, 1.5%	0%		2947	0.48	6203
	21.5%		3149	0.32	9844
Probability of detection SLD, SC, 5.8%	0%		3744	0.54	6997
	25.8%		1610	0.32	5107
Probability of detection CC, SC, 0%	0%		2973	0.45	6537
	20%		2832	0.37	7592
Probability CC+ to HCC, 0.4%	0.34%	Lower limit of 95%CI in [235]	2971	0.46	6529
	0.47%	Upper limit of 95%CI in	2974	0.45	6547

		[235]			
Probability SLD- to HCC, 0.04%	0.03%	Minimal value obtained by combining the factor from 95%CI limits in [236](29.2/2.0=14.6), with probability CC- to HCC, 0.4% (0.03%=0.4%/14.6)	2973	0.45	6534
	0.07%	Maximal value obtained by combining the factor from 95%CI limits in [236] (16.8/2.8=6), with probability CC- to HCC, 0.4% (0.03%=0.4%/6)	2973	0.45	6545
Cut-off age for transition probability to transplant from both DC and HCC	65 yrs	Assumed cut-off for DC to transplant the same as for HCC	2790	0.45	6181
	70 yrs	Assumed cut-off for HCC to transplant the same as for DC	3200	0.46	6975
	80 yrs	Arbitrary	3351	0.46	7261

*The percentage of patients whose alcohol intake decreased to ensure no fibrosis progression and the corresponding mean fibrosis progression rate

8 References

1. Bataller, R. and D.A. Brenner, *Liver fibrosis.* Journal of Clinical Investigation, 2005. **115**(2): p. 209-218.
2. Brunt, E.M., et al., *Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions.* Am J Gastroenterol, 1999. **94**(9): p. 2467-74.
3. Kleiner, D.E., et al., *Design and validation of a histological scoring system for nonalcoholic fatty liver disease.* Hepatology, 2005. **41**(6): p. 1313-21.
4. Bedossa, P. and T. Poynard, *An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group.* Hepatology, 1996. **24**(2): p. 289-93.
5. Thoma, C., C.P. Day, and M.I. Trenell, *Lifestyle interventions for the treatment of non-alcoholic fatty liver disease in adults: a systematic review.* J Hepatol, 2012. **56**(1): p. 255-66.
6. Elpek, G.O., *Cellular and molecular mechanisms in the pathogenesis of liver fibrosis: An update.* World J Gastroenterol, 2014. **20**(23): p. 7260-76.
7. Garcia-Tsao, G. and J. Bosch, *Management of Varices and Variceal Hemorrhage in Cirrhosis.* New England Journal of Medicine, 2010. **362**(9): p. 823-832.
8. Bosch, J., R.J. Groszmann, and V.H. Shah, *Evolution in the understanding of the pathophysiological basis of portal hypertension: How changes in paradigm are leading to successful new treatments.* Journal of Hepatology, 2015. **62**(1, Supplement): p. S121-S130.
9. Tripathi, D., et al., *Randomized controlled trial of carvedilol versus variceal band ligation for the prevention of the first variceal bleed.* Hepatology, 2009. **50**(3): p. 825-33.

10. D'Amico, G., et al., *Hepatic vein pressure gradient reduction and prevention of variceal bleeding in cirrhosis: a systematic review.* Gastroenterology, 2006. **131**(5): p. 1611-24.

11. D'Amico, G., G. Garcia-Tsao, and L. Pagliaro, *Natural history and prognostic indicators of survival in cirrhosis: A systematic review of 118 studies.* Journal of Hepatology, 2006. **44**(1): p. 217-231.

12. de Franchis, R., *Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension.* J Hepatol, 2005. **43**(1): p. 167-76.

13. Fleming, K.M., et al., *The rate of decompensation and clinical progression of disease in people with cirrhosis: a cohort study.* Aliment Pharmacol Ther, 2010. **32**(11-12): p. 1343-50.

14. Fleming, K.M., et al., *All-cause mortality in people with cirrhosis compared with the general population: a population-based cohort study.* Liver Int, 2012. **32**(1): p. 79-84.

15. Ratib, S., et al., *1 and 5 year survival estimates for people with cirrhosis of the liver in England, 1998-2009: a large population study.* J Hepatol, 2014. **60**(2): p. 282-9.

16. Ratib, S., et al., *Diagnosis of liver cirrhosis in England, a cohort study, 1998-2009: a comparison with cancer.* Am J Gastroenterol, 2014. **109**(2): p. 190-8.

17. Murray, C.J., et al., *Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010.* Lancet, 2012. **380**(9859): p. 2197-223.

18. Lozano, R., et al., *Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010.* Lancet, 2012. **380**(9859): p. 2095-128.

19. Mokdad, A.A., et al., *Liver cirrhosis mortality in 187 countries between 1980 and 2010: a systematic analysis.* BMC Med, 2014. **12**: p. 145.

20. Blachier, M., et al., *The burden of liver disease in Europe: a review of available epidemiological data.* J Hepatol, 2013. **58**(3): p. 593-608.

21. Leon, D.A. and J. McCambridge, *Liver cirrhosis mortality rates in Britain from 1950 to 2002: an analysis of routine data.* The Lancet, 2006. **367**(9504): p. 52-56.

22. Williams, R., et al., *Addressing liver disease in the UK: a blueprint for attaining excellence in health care and reducing premature mortality from lifestyle issues of excess consumption of alcohol, obesity, and viral hepatitis.* The Lancet, 2014. **384**(9958): p. 1953-1997.

23. *Mortality statistics: deaths registered in England and Wales (series DR), 2010. Newport, UK: Office for National Statistics.* Office for National Statistics., 2011.

24. Verne, J., *Liver disease: a preventable killer of young adults.* Public Health England (PHE), 2014.

25. *Liver disease: Today's complacency, tomorrow's catastrophe.* The All-Party Parliamentary Hepatology Group (APPHG) Inquiry into improving Outcomes in Liver Disease, 2014.

26. England, P.H., *The 2nd Atlas of variation in risk factors and halthcare for liver disease in England.* 2017.

27. Bhala, N., G. Aithal, and J. Ferguson, *How to tackle rising rates of liver disease in the UK.* BMJ, 2013. **346**: p. f807.

28. Fleming, K.M., et al., *Incidence and prevalence of cirrhosis in the United Kingdom, 1992-2001: a general population-based study.* J Hepatol, 2008. **49**(5): p. 732-8.

29. O'Shea, R.S., et al., *Alcoholic liver disease.* Hepatology, 2010. **51**(1): p. 307-28.

30. Rehm, J., A.V. Samokhvalov, and K.D. Shield, *Global burden of alcoholic liver diseases.* Journal of Hepatology, 2013. **59**(1): p. 160-168.

31. *EASL clinical practical guidelines: management of alcoholic liver disease.* J Hepatol, 2012. **57**(2): p. 399-420.

32. Zatonski, W.A., et al., *Liver cirrhosis mortality in Europe, with special attention to Central and Eastern Europe.* Eur Addict Res, 2010. **16**(4): p. 193-201.

33. Williams, R., et al., *Implementation of the Lancet Standing Commission on Liver Disease in the UK.* The Lancet, 2015. **386**(10008): p. 2098-2111.

34. Sheron, N. and I. Gilmore, *Effect of policy, economics, and the changing alcohol marketplace on alcohol related deaths in England and Wales.* BMJ, 2016. **353**.

35. The Lancet Gastroenterology, H., *Alcohol: are we enjoying responsibly?* Lancet Gastroenterol Hepatol, 2017. **2**(10): p. 691.

36. *Financial case for action on liver disease. Escalating costs of alcohol misuse, obesity and viral hepatitis.* The Lancet commission. UK Liver Disease Crisis. Foundation for liver research. , July 2017.

37. Kaner, E., et al., *Effectiveness of screening and brief alcohol intervention in primary care (SIPS trial): pragmatic cluster randomised controlled trial.* BMJ, 2013. **346**: p. e8501.

38. Health, D.o., *UK Chief Medical Officer's alcohol guidelines review: Summary of the proposed new guidelines.* https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/489795/summary.pdf. Last Accessed 19th March 2018, 2016.

39. *NHS Atlas of Variation in Healthcare for people with Liver disease.* Health Protection Agency 2013.

40. Fuller, E., *Smoking, drinking and drug use among young people in England in 2011.* Health and Social Care Information Centre, 2011.

41. Verrill, C., et al., *Alcohol-related cirrhosis—early abstinence is a key factor in prognosis, even in the most severe cases.* Addiction, 2009. **104**(5): p. 768-774.

42. Kaner, E.F., et al., *Effectiveness of brief alcohol interventions in primary care populations.* Cochrane Database Syst Rev, 2007(2): p. CD004148.

43. Kaner, E.F., et al., *Effectiveness of brief alcohol interventions in primary care populations.* Cochrane Database Syst Rev, 2018. **2**: p. CD004148.

44. Kaner, E., *Brief alcohol intervention: time for translational research.* Addiction, 2010. **105**(6): p. 960-1; discussion 964-5.

45. Ludwig, J., et al., *Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease.* Mayo Clin Proc, 1980. **55**(7): p. 434-8.

46. Whalley, S., et al., *Hepatology outpatient service provision in secondary care: a study of liver disease incidence and resource costs.* Clin Med, 2007. **7**(2): p. 119-24.

47. Chang, Y., et al., *Metabolically Healthy Obesity and the Development of Nonalcoholic Fatty Liver Disease.* Am J Gastroenterol, 2016. **111**(8): p. 1133-40.

48. Wong, V.W.-S., et al., *Incidence of non-alcoholic fatty liver disease in Hong Kong: A population study with paired proton-magnetic resonance spectroscopy.* Journal of Hepatology, 2015. **62**(1): p. 182-189.

49. Browning, J.D., et al., *Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity.* Hepatology, 2004. **40**(6): p. 1387-95.

50. Bedogni, G., et al., *Prevalence of and risk factors for nonalcoholic fatty liver disease: the Dionysos nutrition and liver study.* Hepatology, 2005. **42**(1): p. 44-52.

51. Clark, J.M., F.L. Brancati, and A.M. Diehl, *The prevalence and etiology of elevated aminotransferase levels in the United States.* Am J Gastroenterol, 2003. **98**(5): p. 960-7.

52. Ioannou, G.N., E.J. Boyko, and S.P. Lee, *The prevalence and predictors of elevated serum aminotransferase activity in the United States in 1999-2002.* Am J Gastroenterol, 2006. **101**(1): p. 76-82.

53. Lee, J.Y., et al., *Prevalence and risk factors of non-alcoholic fatty liver disease in potential living liver donors in Korea: a review of 589 consecutive liver biopsies in a single center.* J Hepatol, 2007. **47**(2): p. 239-44.

54. Marcos, A., et al., *Selection and outcome of living donors for adult to adult right lobe transplantation.* Transplantation, 2000. **69**(11): p. 2410-5.

55. Younossi, Z.M., et al., *Global Epidemiology of Non-Alcoholic Fatty Liver Disease-Meta-Analytic Assessment of Prevalence, Incidence and Outcomes.* Hepatology, 2015.

56. Armstrong, M.J., et al., *Presence and severity of non-alcoholic fatty liver disease in a large prospective primary care cohort.* Journal of Hepatology, 2012. **56**(1): p. 234-40.

57. Williams, R., et al., *Disease burden and costs from excess alcohol consumption, obesity, and viral hepatitis: fourth report of the Lancet Standing Commission on Liver Disease in the UK.* Lancet, 2017.

58. Wong, R.J., et al., *Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States.* Gastroenterology, 2015. **148**(3): p. 547-55.

59. Angulo, P., *Long-term mortality in nonalcoholic fatty liver disease: is liver histology of any prognostic significance?* Hepatology, 2010. **51**(2): p. 373-5.

60. Adams, L.A., et al., *Nonalcoholic fatty liver disease increases risk of death among patients with diabetes: a community-based cohort study.* American Journal of Gastroenterology, 2010. **105**(7): p. 1567-73.

61. Ekstedt, M., et al., *Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up.* Hepatology, 2015. **61**(5): p. 1547-54.

62. Ekstedt, M., et al., *Long-term follow-up of patients with NAFLD and elevated liver enzymes.* Hepatology, 2006. **44**(4): p. 865-73.

63. Soderberg, C., et al., *Decreased survival of subjects with elevated liver function tests during a 28-year follow-up.* Hepatology, 2010. **51**(2): p. 595-602.

64. Adams, L.A., et al., *The histological course of nonalcoholic fatty liver disease: a longitudinal study of 103 patients with sequential liver biopsies.* J Hepatol, 2005. **42**(1): p. 132-8.

65. Wong, V.W., et al., *Disease progression of non-alcoholic fatty liver disease: a prospective study with paired liver biopsies at 3 years.* Gut, 2010. **59**(7): p. 969-74.

66. McPherson, S., et al., *Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management.* J Hepatol, 2015. **62**(5): p. 1148-55.

67. Hagstrom, H., et al., *Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD.* J Hepatol, 2017. **67**(6): p. 1265-1273.

68. Dulai, P.S., et al., *Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis.* Hepatology, 2017. **65**(5): p. 1557-1565.

69. Ng, M., et al., *Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013.* The Lancet, 2014. **384**(9945): p. 766-781.

70. Newton, J.N., et al., *Changes in health in England, with analysis by English regions and areas of deprivation, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013.* The Lancet. **386**(10010): p. 2257-2274.

71. *NHS Digital. Health Survey for England, 2015.* www.content.digital.nhs.uk/catalogue/PUB22610, 2016.

72. Wang, Y.C., et al., *Health and economic burden of the projected obesity trends in the USA and the UK.* Lancet, 2011. **378**(9793): p. 815-25.

73. UK, D., *Diabetes: Facts and Stats.* 2014.

74. Gatineau M, H.C., Holman N, Outhwaite H, and C.A. Oldridge L, Ells L., *Adult obesity and type 2 diabetes.* Oxford: Public Health England, 2014.

75. Younossi, Z.M., et al., *The Economic and Clinical Burden of Non-alcoholic Fatty Liver Disease (NAFLD) in the United States and Europe.* Hepatology, 2016: p. n/a-n/a.

76. Scarborough, P., et al., *The economic burden of ill health due to diet, physical inactivity, smoking, alcohol and obesity in the UK: an update to 2006-07 NHS costs.* J Public Health (Oxf), 2011. **33**(4): p. 527-35.

77. Hex, N., et al., *Estimating the current and future costs of Type 1 and Type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs.* Diabet Med, 2012. **29**(7): p. 855-62.

78. McLernon, D.J., et al., *Health outcomes following liver function testing in primary care: a retrospective cohort study.* Fam Pract, 2009. **26**(4): p. 251-9.

79. group, N.N.C.C.c., *Connect Medical.* 2012(1): p. 1-4.

80. George, K., *Management of abnormal LFT in asympotmatic patients.* BSG Guidelines.

81. Fracanzani, A.L., et al., *Risk of severe liver disease in nonalcoholic fatty liver disease with normal aminotransferase levels: a role for insulin resistance and diabetes.* Hepatology, 2008. **48**(3): p. 792-8.

82. Skelly, M.M., P.D. James, and S.D. Ryder, *Findings on liver biopsy to investigate abnormal liver function tests in the absence of diagnostic serology.* J Hepatol, 2001. **35**(2): p. 195-9.

83. Newsome, P.N., et al., *Guidelines on the management of abnormal liver blood tests.* Gut, 2018. **67**(1): p. 6-19.

84. Donnan, P.T., et al., *Development of a decision support tool for primary care management of patients with abnormal liver function tests without clinically apparent liver disease: a record-linkage population cohort study and decision analysis (ALFIE).* Health Technol Assess, 2009. **13**(25): p. iii-iv, ix-xi, 1-134.

85. Sanyal, A.J., et al., *Similarities and differences in outcomes of cirrhosis due to nonalcoholic steatohepatitis and hepatitis C.* Hepatology, 2006. **43**(4): p. 682-9.

86. Angulo, P., et al., *Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis.* Hepatology, 1999. **30**(6): p. 1356-62.

87. Mofrad, P., et al., *Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values.* Hepatology, 2003. **37**(6): p. 1286-1292.

88. Prati, D., et al., *Updated definitions of healthy ranges for serum alanine aminotransferase levels.* Ann Intern Med, 2002. **137**(1): p. 1-10.

89. Kunde, S.S., et al., *Spectrum of NAFLD and diagnostic implications of the proposed new normal range for serum ALT in obese women.* Hepatology, 2005. **42**(3): p. 650-6.

90. Saadeh, S., et al., *The utility of radiological imaging in nonalcoholic fatty liver disease.* Gastroenterology, 2002. **123**(3): p. 745-50.

91. Joy, D., V.R. Thava, and B.B. Scott, *Diagnosis of fatty liver disease: is biopsy necessary?* Eur J Gastroenterol Hepatol, 2003. **15**(5): p. 539-43.

92. Martin, J., et al., *Accuracy of Ultrasound and Noninvasive Markers of Fibrosis to Identify Patients with Cirrhosis.* Digestive Diseases and Sciences, 2015: p. 1-7.

93. Cadranel, J.F., P. Rufat, and F. Degos, *Practices of liver biopsy in France: results of a prospective nationwide survey. For the Group of Epidemiology of the French Association for the Study of the Liver (AFEF).* Hepatology, 2000. **32**(3): p. 477-81.

94. Howlett, D.C., et al., *Findings of the UK National Audit Evaluating Image-guided or Image-assisted Liver Biopsy. Part II. Minor and Major Complications and Procedure-related Mortality.* Radiology, 2013. **266**(1): p. 226-235.

95. West, J. and T.R. Card, *Reduced mortality rates following elective percutaneous liver biopsies.* Gastroenterology, 2010. **139**(4): p. 1230-7.

96. Beckmann, M.G., et al., *Clinical relevance of transjugular liver biopsy in comparison with percutaneous and laparoscopic liver biopsy.* Gastroenterol Res Pract, 2009. **2009**: p. 947014.

97. *National Schedule of Reference Costs 2012-2013 for NHS trusts and NHS foundation trusts.* Department of Health, 2012-2013. **Last accessed 10th September 2015**.

98. Ratziu, V., et al., *Sampling variability of liver biopsy in nonalcoholic fatty liver disease.* Gastroenterology, 2005. **128**(7): p. 1898-906.

99. Davies, S.C., *Annual report of the Chief Medical Officer, Volume One, 2011. On the State of the Public's Health.* London: Department of Health, 2012. **Volume one and two**: p. 162-165.

100. Swinburn, B.A., et al., *The global obesity pandemic: shaped by global drivers and local environments.* Lancet, 2011. **378**(9793): p. 804-14.

101. The Lancet, G., amp, and Hepatology, *Minimum alcohol pricing in Scotland.* The Lancet Gastroenterology & Hepatology. **3**(1): p. 1.

102. *Soft Drinks Industry Levy. HM Revenue & Customs UK Government.* https://www.gov.uk/topic/business-tax/soft-drinks-industry-levy. Last accessed 5th August 2018.

103. Ratziu, V., et al., *A position statement on NAFLD/NASH based on the EASL 2009 special conference.* Journal of Hepatology, 2010. **53**(2): p. 372-384.

104. Chalasani, N., et al., *The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases.* Hepatology, 2018. **67**(1): p. 328-357.

105. *EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease.* J Hepatol, 2016. **64**(6): p. 1388-402.

106. Vergniol, J., et al., *Evolution of noninvasive tests of liver fibrosis is associated with prognosis in patients with chronic hepatitis C.* Hepatology, 2014. **60**(1): p. 65-76.

107. Boursier, J., et al., *Diagnostic accuracy and prognostic significance of blood fibrosis tests and liver stiffness measurement by FibroScan in non-alcoholic fatty liver disease.* J Hepatol, 2016.

108. *Biomarkers and surrogate endpoints: preferred definitions and conceptual framework.* Clin Pharmacol Ther, 2001. **69**(3): p. 89-95.

109. Sandrin, L., et al., *Transient elastography: a new noninvasive method for assessment of hepatic fibrosis.* Ultrasound Med Biol, 2003. **29**(12): p. 1705-13.

110. Friedrich-Rust, M., et al., *Performance of transient elastography for the staging of liver fibrosis: a meta-analysis.* Gastroenterology, 2008. **134**(4): p. 960-74.

111. Boursier, J., et al., *Determination of reliability criteria for liver stiffness evaluation by transient elastography.* Hepatology, 2013. **57**(3): p. 1182-91.

112. Roulot, D., et al., *Transient elastography as a screening tool for liver fibrosis and cirrhosis in a community-based population aged over 45 years.* Gut, 2011. **60**(7): p. 977-84.

113. Moessner, B.K., et al., *Outreach screening of drug users for cirrhosis with transient elastography.* Addiction, 2011. **106**(5): p. 970-6.

114. Myers, R.P., et al., *Feasibility and diagnostic performance of the FibroScan XL probe for liver stiffness measurement in overweight and obese patients.* Hepatology, 2012. **55**(1): p. 199-208.

115. Bardou-Jacquet, E., et al., *Effect of alcohol consumption on liver stiffness measured by transient elastography.* World J Gastroenterol, 2013. **19**(4): p. 516-22.

116. Millonig, G., et al., *Liver stiffness is directly influenced by central venous pressure.* Journal of Hepatology, 2010. **52**(2): p. 206-210.

117. Millonig, G., et al., *Extrahepatic cholestasis increases liver stiffness (FibroScan) irrespective of fibrosis.* Hepatology, 2008. **48**(5): p. 1718-23.

118. Rosenberg, W.M., et al., *Serum markers detect the presence of liver fibrosis: a cohort study.* Gastroenterology, 2004. **127**(6): p. 1704-13.

119. Guha, I.N., et al., *Noninvasive markers of fibrosis in nonalcoholic fatty liver disease: Validating the European Liver Fibrosis Panel and exploring simple markers.* Hepatology, 2008. **47**(2): p. 455-60.

120. Parkes, J., et al., *Enhanced Liver Fibrosis (ELF) test accurately identifies liver fibrosis in patients with chronic hepatitis C.* J Viral Hepat, 2011. **18**(1): p. 23-31.

121. Parkes, J., et al., *Enhanced liver fibrosis test can predict clinical outcomes in patients with chronic liver disease.* Gut, 2010. **59**(9): p. 1245-51.

122. McPherson, S., et al., *Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease.* Gut, 2010. **59**(9): p. 1265-9.

123. Harrison, S.A., et al., *Development and validation of a simple NAFLD clinical scoring system for identifying patients without advanced disease.* Gut, 2008. **57**(10): p. 1441-7.

124. Shah, A.G., et al., *Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease.* Clin Gastroenterol Hepatol, 2009. **7**(10): p. 1104-12.

125. Sheth, S.G., et al., *AST/ALT ratio predicts cirrhosis in patients with chronic hepatitis C virus infection.* Am J Gastroenterol, 1998. **93**(1): p. 44-8.

126. Ratziu, V., et al., *Liver fibrosis in overweight patients.* Gastroenterology, 2000. **118**(6): p. 1117-23.

127. Angulo, P., et al., *The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD.* Hepatology, 2007. **45**(4): p. 846-54.

128. Cales, P., et al., *Evaluating the accuracy and increasing the reliable diagnosis rate of blood tests for liver fibrosis in chronic hepatitis C.* Liver Int, 2008. **28**(10): p. 1352-62.

129. Ratziu, V., et al., *Diagnostic value of biochemical markers (FibroTest-FibroSURE) for the prediction of liver fibrosis in patients with non-alcoholic fatty liver disease.* BMC Gastroenterol, 2006. **6**: p. 6.

130. Tanwar, S., et al., *Validation of terminal peptide of procollagen III for the detection and assessment of nonalcoholic steatohepatitis in patients with nonalcoholic fatty liver disease.* Hepatology, 2013. **57**(1): p. 103-11.

131. Wang, Q.B., et al., *Performance of magnetic resonance elastography and diffusion-weighted imaging for the staging of hepatic fibrosis: A meta-analysis.* Hepatology, 2012. **56**(1): p. 239-47.

132. Chen, J., et al., *Early detection of nonalcoholic steatohepatitis in patients with nonalcoholic fatty liver disease by using MR elastography.* Radiology, 2011. **259**(3): p. 749-56.

133. Liu, H., et al., *Acoustic Radiation Force Impulse Elastography for the Non-Invasive Evaluation of Hepatic Fibrosis in Non-Alcoholic Fatty Liver Disease Patients: A Systematic Review & Meta-Analysis.* PLOS ONE, 2015. **10**(7): p. e0127782.

134. Yoneda, M., et al., *Nonalcoholic fatty liver disease: US-based acoustic radiation force impulse elastography.* Radiology, 2010. **256**(2): p. 640-7.

135. Singh, S., et al., *Diagnostic Performance of Magnetic Resonance Elastography in Staging Liver Fibrosis: A Systematic Review and Meta-analysis of Individual Participant Data.* Clin Gastroenterol Hepatol, 2015. **13**(3): p. 440-451 e6.

136. Banerjee, R., et al., *Multiparametric magnetic resonance for the non-invasive diagnosis of liver disease.* J Hepatol, 2014. **60**(1): p. 69-77.

137. Hoad CL, P.N., Kaye P, Bawden S, Stephenson M, Dolman GE, James MW, Costigan C, Austin A, Chernova-Chernaya Y, Gowland PA, Guha IN, Francis ST, Aithal GP, *Quantitative Magnetic Resonance Imaging (MRI) in the evaluation of the degree of*

steatosis, iron accumulation and fibrosis in chronic liver disease (MRker study). Journal of Hepatology 2013. **58(S1): S285-6**.

138. Friedrich-Rust, M., et al., *Comparison of ELF, FibroTest and FibroScan for the non-invasive assessment of liver fibrosis.* BMC Gastroenterol, 2010. **10**: p. 103.

139. Wong, V.W., et al., *Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease.* Hepatology, 2010. **51**(2): p. 454-62.

140. Nguyen-Khac, E., et al., *Assessment of asymptomatic liver fibrosis in alcoholic patients using fibroscan: prospective comparison with seven non-invasive laboratory tests.* Aliment Pharmacol Ther, 2008. **28**(10): p. 1188-98.

141. Ransohoff, D.F. and A.R. Feinstein, *Problems of spectrum and bias in evaluating the efficacy of diagnostic tests.* N Engl J Med, 1978. **299**(17): p. 926-30.

142. Usher-Smith, J.A., Sharp, Stephen J, and S.J. Griffin, *The spectrum effect in tests for risk prediction, screening, and diagnosis.* BMJ, 2016. **353**.

143. *Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015.* Lancet, 2016. **388**(10053): p. 1459-1544.

144. *Cochrane Handbook for Systematic Reviews of Interventions.* The Cochrane Collaboration, 2011. **Version 5.1.0**.

145. Liberati, A., et al., *The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration.* J Clin Epidemiol, 2009. **62**(10): p. e1-34.

146. You, S.C., et al., *Factors associated with significant liver fibrosis assessed using transient elastography in general population.* World J Gastroenterol, 2015. **21**(4): p. 1158-66.

147. Baba, M., et al., *Discrimination of individuals in a general population at high-risk for alcoholic and non-alcoholic fatty liver disease based on liver stiffness: a cross section study.* BMC Gastroenterol, 2011. **11**: p. 70.

148. Wong, V.W., et al., *Prevalence of non-alcoholic fatty liver disease and advanced fibrosis in Hong Kong Chinese: a population study using proton-magnetic resonance spectroscopy and transient elastography.* Gut, 2012. **61**(3): p. 409-15.

149. Veysey, M., et al., *Hepatic fibrosis in an elderly population.* Journal of Gastroenterology and Hepatology (Australia), 2014. **29**: p. 87.

150. Williamson, R.M., et al., *Prevalence and markers of advanced liver disease in type 2 diabetes.* QJM, 2012. **105**(5): p. 425-32.

151. Morling, J.R., et al., *Using non-invasive biomarkers to identify hepatic fibrosis in people with type 2 diabetes mellitus: the Edinburgh type 2 diabetes study.* J Hepatol, 2014. **60**(2): p. 384-91.

152. Das, K., et al., *Nonobese population in a developing country has a high prevalence of nonalcoholic fatty liver and significant liver disease.* Hepatology, 2010. **51**(5): p. 1593-1602.

153. Sheron, N., et al., *Feasibility of detection and intervention for alcohol-related liver disease in the community: the Alcohol and Liver Disease Detection study (ALDDeS).* Br J Gen Pract, 2013. **63**(615): p. e698-705.

154. Poynard, T., et al., *Prevalence of liver fibrosis and risk factors in a general population using non-invasive biomarkers (FibroTest).* BMC Gastroenterol, 2010. **10**: p. 40.

155. Malik R., M.R.P., Cheshire L., Jalan R. , *Development and evaluation of a liver health programme for asymptomatic subjects at risk of liver disease.* Conference: 60th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2009 Boston, MA United States., 2009.

156. Zelber-Sagi, S., et al., *The association between adipocytokines and biomarkers for nonalcoholic fatty liver disease-induced liver injury: a study in the general population.* Eur J Gastroenterol Hepatol, 2012. **24**(3): p. 262-9.

157. Harman, D.J., et al., *Direct targeting of risk factors significantly increases the detection of liver cirrhosis in primary care: a cross-sectional diagnostic study utilising transient elastography.* BMJ Open, 2015. **5**(4): p. e007516.

158. Nahon, P., et al., *Assessment of liver fibrosis using transient elastography in patients with alcoholic liver disease.* J Hepatol, 2008. **49**(6): p. 1062-8.

159. Grattagliano I, U.E., Napoli L, Marulli CF, Nebiacolombo C, Cottone C, et al, *Utility of noninvasive methods for the characterization of nonalcoholic liver steatosis in the family practice. The "VARES" Italian multicenter study. .* Ann Hepatol. . **2013 Jan-Feb;12(1):70-7.**

160. Lemoine, M., et al., *Food intake increases liver stiffness measurements and hampers reliable values in patients with chronic hepatitis B and healthy controls: the PROLIFICA experience in The Gambia.* Alimentary Pharmacology & Therapeutics, 2014. **39**(2): p. 188-96.

161. Fabrellas, N., et al., *Using transient elastography to detect chronic liver diseases in a primary care nurse consultancy.* Nurs Res, 2013. **62**(6): p. 450-4.

162. Kim, D., et al., *Association between noninvasive fibrosis markers and mortality among adults with nonalcoholic fatty liver disease in the United States.* Hepatology, 2013. **57**(4): p. 1357-65.

163. Jepsen, P., H. Vilstrup, and H.T. Sørensen, *Alcoholic cirrhosis in Denmark – population-based incidence, prevalence, and hospitalization rates between 1988 and 2005: A descriptive cohort study.* BMC Gastroenterology, 2008. **8**: p. 3-3.

164. Roulot, D., et al., *Liver stiffness values in apparently healthy subjects: influence of gender and metabolic syndrome.* J Hepatol, 2008. **48**(4): p. 606-13.

165. Conti, F., et al., *Transient elastography in healthy subjects and factors influencing liver stiffness in non-alcoholic fatty liver disease: An Italian community-based population study.* Digestive and Liver Disease, 2016. **48**(11): p. 1357-1363.

166. Das, K., et al., *"Normal" liver stiffness measure (LSM) values are higher in both lean and obese individuals: a population-based study from a developing country.* Hepatology, 2012. **55**(2): p. 584-93.

167. Mueller, S., et al., *Increased liver stiffness in alcoholic liver disease: differentiating fibrosis from steatohepatitis.* World J Gastroenterol, 2010. **16**(8): p. 966-72.

168. *EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease.* J Hepatol, 2016.

169. You, S.C., et al., *Factors associated with significant liver fibrosis assessed using transient elastography in general population.* World J Gastroenterol, 2015. **21**(4): p. 1158-66.

170. Alberti, K.G., et al., *Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity.* Circulation, 2009. **120**(16): p. 1640-5.

171. Marchesini, G., et al., *Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome.* Hepatology, 2003. **37**(4): p. 917-923.

172. Liu, B., et al., *Body mass index and risk of liver cirrhosis in middle aged UK women: prospective study.* BMJ, 2010. **340**: p. c912.

173. Hart, C.L., et al., *Effect of body mass index and alcohol consumption on liver disease: analysis of data from two prospective cohort studies.* BMJ, 2010. **340**: p. c1240.

174. Harris, R., et al., *Prevalence of clinically significant liver disease within the general population, as defined by non-invasive markers of liver fibrosis: a systematic review.* Lancet Gastroenterol Hepatol, 2017. **2**(4): p. 288-297.

175. Harman, D.J., et al., *Obesity and type 2 diabetes are important risk factors underlying previously undiagnosed cirrhosis in general practice: a cross-sectional study using transient elastography.* Aliment Pharmacol Ther, 2017.

176. *Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies.* Lancet, 2004. **363**(9403): p. 157-63.

177. Fagan, K.J., et al., *ELF score >/=9.8 indicates advanced hepatic fibrosis and is influenced by age, steatosis and histological activity.* Liver Int, 2015. **35**(6): p. 1673-81.

178. Lichtinghagen, R., et al., *The Enhanced Liver Fibrosis (ELF) score: Normal values, influence factors and proposed cut-off values.* Journal of Hepatology, 2013. **59**(2): p. 236-242.

179. *UK Census Data 2011.* http://www.ukcensusdata.com/knighton-e05001797/ethnic-group-qs201ew. Last accessed 7th February 2018.

180. Logan, R.F.A., et al., *Outcomes of the Bowel Cancer Screening Programme (BCSP) in England after the first 1 million tests.* Gut, 2012. **61**(10): p. 1439-1446.

181. Boursier, J., et al., *Precise evaluation of liver histology by computerized morphometry shows that steatosis influences liver stiffness measured by transient elastography in chronic hepatitis C.* J Gastroenterol, 2014. **49**(3): p. 527-37.

182. Eddowes, P., et al., *Performance of liver stiffness by Fibroscan in a Large Prospective Multicentre UK Study: Applicability, Reliability, Diagnostic Perforamce and Influence of the Probe Type and Of Steatosis on the Liver Stiffness Measurement. Oral Abstracts (Abstracts 1–263).* Hepatology, 2017. **66**: p. 1-148.

183. (NICE), N.I.f.H.C.a.E., *Non-alcoholic fatty liver disease (NAFLD): assessment and management.* 2016.

184. *NICE National Institute for Health and Care Excellence. Cirrhosis in over 16s: assessment and management. nice.org.uk/guidance/ng50.* July 2016.

185. Thiele, M., et al., *Accuracy of the Enhanced Liver Fibrosis Test Vs FibroTest, Elastography, and Indirect Markers in Detection of Advanced Fibrosis in Patients With Alcoholic Liver Disease.* Gastroenterology, 2018.

186. *NHS Digital. Health Survey for England, 2015 [NS].* www.content.digital.nhs.uk/catalogue/PUB22610, Publication date: December 14, 2016.

187. Hudson, M., et al., *Should we screen for cirrhosis?* BMJ, 2017. **358**.

188. Promrat, K., et al., *Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis.* Hepatology, 2010. **51**(1): p. 121-9.

189. Vilar-Gomez, E., et al., *Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis.* Gastroenterology, 2015. **149**(2): p. 367-78 e5; quiz e14-5.

190. Lazo, M., et al., *Effect of a 12-month intensive lifestyle intervention on hepatic steatosis in adults with type 2 diabetes.* Diabetes Care, 2010. **33**(10): p. 2156-63.

191. Day, C.P., *Who gets alcoholic liver disease: nature or nurture?* J R Coll Physicians Lond, 2000. **34**(6): p. 557-62.

192. Portillo-Sanchez, P., et al., *High Prevalence of Nonalcoholic Fatty Liver Disease in Patients With Type 2 Diabetes Mellitus and Normal Plasma Aminotransferase Levels.* J Clin Endocrinol Metab, 2015. **100**(6): p. 2231-8.

193. EASL, *EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis.* J Hepatol, 2015. **63**(1): p. 237-64.

194. Castera, L., et al., *Pitfalls of liver stiffness measurement: a 5-year prospective study of 13,369 examinations.* Hepatology, 2010. **51**(3): p. 828-35.

195. Foucher, J., et al., *Prevalence and factors associated with failure of liver stiffness measurement using FibroScan in a prospective study of 2114 examinations.* Eur J Gastroenterol Hepatol, 2006. **18**(4): p. 411-2.

196. Tapper, E.B., et al., *The Performance of Vibration Controlled Transient Elastography in a US Cohort of Patients With Nonalcoholic Fatty Liver Disease.* Am J Gastroenterol, 2016. **111**(5): p. 677-84.

197. *Statistics on obesity, physical activity and diet.* Health and Social Care Information Centre. Government statistical service, 28th April 2016.

198. Echosens, *FibroScan Recommendations: Updated recommendations for a reliable FibroScan® liver stiffness measurement.* www.Echosens.com.

199. de Ledinghen, V., et al., *Diagnosis of liver fibrosis and cirrhosis using liver stiffness measurement: comparison between M and XL probe of FibroScan(R).* J Hepatol, 2012. **56**(4): p. 833-9.

200. Friedrich-Rust, M., et al., *Transient elastography with a new probe for obese patients for non-invasive staging of non-alcoholic steatohepatitis.* Eur Radiol, 2010. **20**(10): p. 2390-6.

201. Standish, R.A., et al., *An appraisal of the histopathological assessment of liver fibrosis.* Gut, 2006. **55**(4): p. 569-578.

202. Eddowes, P., et al., *Steatosis and liver stiffness measurements using transient elastography.* Hepatology, 2016. **64**(2): p. 700.

203. Puigvehi, M., et al., *Impact of anthropometric features on the applicability and accuracy of FibroScan((R)) (M and XL) in overweight/obese patients.* J Gastroenterol Hepatol, 2017. **32**(10): p. 1746-1753.

204. Sporea, I., et al., *Feasibility of Transient Elastography with M and XL probes in real life.* Med Ultrason, 2016. **18**(1): p. 7-10.

205. Vuppalanchi, R., et al., *Performance characteristics of vibration-controlled transient elastography for evaluation of nonalcoholic fatty liver disease.* Hepatology, 2017.

206. PPPHG, *Liver disease: Today's complacency, tomorrow's catastrophe.* The All-Party Parliamentary Hepatology Group (APPHG) Inquiry into improving Outcomes in Liver Disease, 2014.

207. *EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease.* Journal of Hepatology, 2016. **64**(6): p. 1388-1402.

208. Husereau, D., et al., *Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement.* PharmacoEconomics, 2013. **31**(5): p. 361-367.

209. Saunders, J.B., et al., *Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II.* Addiction, 1993. **88**(6): p. 791-804.

210. NICE, *Alcohol use disorders: diagnosis, assessment and management of harful drinking and alcohol dependence.* NICE clinical guideline 115, 2011.

211. Euroqol Group. *Measuring Self-Reported Population Health-An International Perspective based on EQ-5D*. 2008; Available from: http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Books/Measuring_Self-Reported_Population_Health_-_An_International_Perspective_based_on_EQ-5D.pdf.

212. Department of Health, *NHS Reference Costs 2013 to 2014*. 2014.

213. PSSRU, *Unit Costs of Health & Social Care 2014*. 2014.

214. National Institute for Health and Clinical Excellence, *The guidelines manual*. 2007: London.

215. Singh, S., et al., *Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies.* Clin Gastroenterol Hepatol, 2015. **13**(4): p. 643-54 e1-9; quiz e39-40.

216. Musso, G., et al., *A meta-analysis of randomized trials for the treatment of nonalcoholic fatty liver disease.* Hepatology, 2010. **52**(1): p. 79-104.

217. Aithal, G.P., et al., *Randomized, placebo-controlled trial of pioglitazone in nondiabetic subjects with nonalcoholic steatohepatitis.* Gastroenterology, 2008. **135**(4): p. 1176-84.

218. Sanyal, A.J., et al., *Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis.* N Engl J Med, 2010. **362**(18): p. 1675-85.

219. Ratziu, V., et al., *Rosiglitazone for Nonalcoholic Steatohepatitis: One-Year Results of the Randomized Placebo-Controlled Fatty Liver Improvement With Rosiglitazone Therapy (FLIRT) Trial.* Gastroenterology, 2008. **135**(1): p. 100-110.

220. Kon, P., *Avandia and Avandamet (rosiglitazone). Suspension of marketing: benefits no longer outweigh risks. Letter for healthcare professionals.* http://webarchive.nationalarchives.gov.uk/20141205150130/http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON096743. *Last accessed 11/03/2016.* 2010.

221. Mahady, S.E., et al., *Pioglitazone and vitamin E for nonalcoholic steatohepatitis: a cost utility analysis.* Hepatology, 2012. **56**(6): p. 2172-9.

222. Bhala, N., et al., *The natural history of nonalcoholic fatty liver disease with advanced fibrosis or cirrhosis: An international collaborative study.* Hepatology, 2011. **54**(4): p. 1208-1216.

223. Holman, R.R., et al., *10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes.* New England Journal of Medicine, 2008. **359**(15): p. 1577-1589.

224. Sanyal, A.J., et al., *Similarities and differences in outcomes of cirrhosis due to nonalcoholic steatohepatitis and hepatitis C.* Hepatology, 2006. **43**(4): p. 682-689.

225. Ascha, M.S., et al., *The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis.* Hepatology, 2010. **51**(6): p. 1972-1978.

226. Ratziu, V., et al., *Survival, liver failure, and hepatocellular carcinoma in obesity-related cryptogenic cirrhosis.* Hepatology, 2002. **35**(6): p. 1485-1493.

227. Lang, K., et al., *The burden of illness associated with hepatocellular carcinoma in the United States.* Journal of Hepatology. **50**(1): p. 89-99.

228. Altekruse, S.F., K.A. McGlynn, and M.E. Reichman, *Hepatocellular Carcinoma Incidence, Mortality, and Survival Trends in the United States From 1975 to 2005.* Journal of Clinical Oncology, 2009. **27**(9): p. 1485-1491.

229. Wang, X., et al., *Outcomes of Liver Transplantation for Nonalcoholic Steatohepatitis: A Systematic Review and Meta-analysis.* Clinical Gastroenterology and Hepatology. **12**(3): p. 394-402.e1.

230. Mathurin, P., et al., *Fibrosis progression occurs in a subgroup of heavy drinkers with typical histological features.* Alimentary Pharmacology & Therapeutics, 2007. **25**(9): p. 1047-1054.

231. Naveau, S., et al., *Biomarkers for the prediction of liver fibrosis in patients with chronic alcoholic liver disease.* Clinical Gastroenterology and Hepatology. **3**(2): p. 167-174.

232. Calès, P., et al., *A novel panel of blood markers to assess the degree of liver fibrosis.* Hepatology, 2005. **42**(6): p. 1373-1381.

233. Nguyen-Khac, E., et al., *Assessment of asymptomatic liver fibrosis in alcoholic patients using fibroscan: prospective comparison with seven non-invasive laboratory tests.* Alimentary Pharmacology & Therapeutics, 2008. **28**(10): p. 1188-1198.

234. Kaner, E., et al., *Effectiveness of screening and brief alcohol intervention in primary care (SIPS trial): pragmatic cluster randomised controlled trial*. Vol. 346. 2013.

235. Jepsen, P., et al., *Risk for Hepatocellular Carcinoma in Patients With Alcoholic CirrhosisA Danish Nationwide Cohort Study.* Annals of Internal Medicine, 2012. **156**(12): p. 841-847.

236. Kuper, H., et al., *The risk of liver and bile duct cancer in patients with chronic viral hepatitis, alcoholism, or cirrhosis.* Hepatology, 2001. **34**(4): p. 714-718.

237. Solà, R., et al., *Probability of liver cancer and survival in HCV-related or alcoholic-decompensated cirrhosis. A study of 377 patients.* Liver International, 2006. **26**(1): p. 62-72.

238. Perry, J.F., et al., *Outcome of patients with hepatocellular carcinoma referred to a tertiary centre with availability of multiple treatment options including cadaveric liver transplantation.* Liver International, 2007. **27**(9): p. 1240-1248.

239. Burra, P., et al., *Liver Transplantation for Alcoholic Liver Disease in Europe: A Study from the ELTR (European Liver Transplant Registry).* American Journal of Transplantation, 2010. **10**(1): p. 138-148.

240. Gough, S.C.L., et al., *Impact of obesity and type 2 diabetes on health-related quality of life in the general population in England.* Diabetes Metab Syndr Obes, 2009. **2**: p. 179-84.

241. Chong, C.A., et al., *Health-state utilities and quality of life in hepatitis C patients.* Am J Gastroenterol, 2003. **98**(3): p. 630-8.

242. Tsochatzis, E.A., et al., *Cost-effectiveness of noninvasive liver fibrosis tests for treatment decisions in patients with chronic hepatitis C.* Hepatology, 2014. **60**(3): p. 832-43.

243. Tapper, E.B., et al., *Cost-Effective Evaluation of Nonalcoholic Fatty Liver Disease With NAFLD Fibrosis Score and Vibration Controlled Transient Elastography.* Am J Gastroenterol, 2015. **110**(9): p. 1298-304.

244. Crossan, C., et al., *Cost-effectiveness of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease: systematic review and economic evaluation.* Health Technol Assess, 2015. **19**(9): p. 1-410.

245. Steadman, R., et al., *A health technology assessment of transient elastography in adult liver disease.* Can J Gastroenterol, 2013. **27**(3): p. 149-58.

246. Ratziu, V., et al., *A position statement on NAFLD/NASH based on the EASL 2009 special conference.* J Hepatol, 2010. **53**(2): p. 372-84.

247. Lin, Y.C., H.M. Lo, and J.D. Chen, *Sonographic fatty liver, overweight and ischemic heart disease.* World J Gastroenterol, 2005. **11**(31): p. 4838-42.

248. Ratziu, V., et al., *Sampling Variability of Liver Biopsy in Nonalcoholic Fatty Liver Disease.* Gastroenterology, 2005. **128**(7): p. 1898-1906.

249. Musso, G., et al., *Meta-analysis: Natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity.* Annals of Medicine, 2011. **43**(8): p. 617-649.

250. Georgescu, E.F., et al., *Angiotensin-receptor blockers as therapy for mild-to-moderate hypertension-associated non-alcoholic steatohepatitis.* World J Gastroenterol, 2009. **15**(8): p. 942-54.

251. Cusi, K., et al., *Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes MellitusA Randomized, Controlled TrialLong-Term Pioglitazone for Patients With NASH and Prediabetes or T2DM.* Annals of Internal Medicine, 2016. **N/A**(N/A): p. N/A-N/A.

252. Dawson, D.A., et al., *Recovery from DSM-IV alcohol dependence: United States, 2001-2002.* Addiction, 2005. **100**(3): p. 281-92.

253. Boursier, J., et al., *Diagnostic accuracy and prognostic significance of blood fibrosis tests and liver stiffness measurement by FibroScan in non-alcoholic fatty liver disease.* Journal of Hepatology, 2016. **65**(3): p. 570-8.

254. Longworth, L., et al., *Midterm cost-effectiveness of the liver transplantation program of England and Wales for three disease groups.* Liver Transpl, 2003. **9**(12): p. 1295-307.

255. Ouwens, J.P., et al., *The cost effectiveness of lung transplantation compared with that of heart and liver transplantation in the Netherlands.* Transpl Int, 2003. **16**(2): p. 123-7.

256. Harman, D.J., *Economic modelling of early TIPS insertion for acute variceal haemorrhage.* (Available from authors on request), 2014.

257. Stamuli, E., *Cost-effectiveness of ultrasound elastography in the assessment of liver fibrosis*, in *Centre for Evidence-Based Purchasing Economic Report*. 2009.

258. Wright, M., et al., *Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation.* Health Technol Assess, 2006. **10**(21): p. 1-113, iii.

259. Thompson Coon, J., et al., *Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis.* Health Technol Assess, 2007. **11**(34): p. 1-206.

260. NICE, *Alcohol-use disorders: alcohol dependence. Costing report*. 2011.

261. Chalasani, N., et al., *The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association.* Hepatology, 2012. **55**(6): p. 2005-23.

262. George K, R.S., Collier J, Chapman R, Freeman J., *Management of abnormal LFT in asympotmatic patients.* BSG Guidelines.

263. Professor James Neuberger, D.A.G., Professor Chris DAy, Dr Sushma Saxseena, *Guidelines on the use of Liver Biopsy in Clinical Practice. BSG Guidelines in Gastroenterology.* 2004.

264. Tripathi, *UK Guidelines on the management of variceal bleeding in cirrhotic patients.* BSG guidelines, 2015.

265. EASL, *EASL-EORTC Clinical Practice Guidelines: Managment of Hepatocellular Carcinoma.* Journal of Hepatology, 2012. **Vol. 56**: p. 908-943.

266. Ratziu, V., et al., *Rosiglitazone for nonalcoholic steatohepatitis: one-year results of the randomized placebo-controlled Fatty Liver Improvement with Rosiglitazone Therapy (FLIRT) Trial.* Gastroenterology, 2008. **135**(1): p. 100-10.

267. Moore, K.P. and G.P. Aithal, *Guidelines on the management of ascites in cirrhosis.* Gut, 2006. **55 Suppl 6**: p. vi1-12.

268. American Association for the Study of Liver, D. and L. European Association for the Study of the, *Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases.* J Hepatol, 2014. **61**(3): p. 642-59.

269. Bennett, W.G., et al., *Estimates of the cost-effectiveness of a single course of interferon-alpha 2b in patients with histologically mild chronic hepatitis C.* Ann Intern Med, 1997. **127**(10): p. 855-65.

270. NICE, *Rifaximin for preventing episodes of overt hepatic encephalopathy.* NICE technology appraisal guidance 337, 2015.

271. Short, J.B., E, James, M, *HCC in 2010; are we offering the appropriate therapy?* BSG 2011 Abstract submission, 2011.

272. Imamura, H., et al., *Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy.* J Hepatol, 2003. **38**(2): p. 200-7.

273. D'Amico, G., et al., *Competing risks and prognostic stages of cirrhosis: a 25-year inception cohort study of 494 patients.* Aliment Pharmacol Ther, 2014. **39**(10): p. 1180-93.

274. Schutte, K., et al., *Characterization and prognosis of patients with hepatocellular carcinoma (HCC) in the non-cirrhotic liver.* BMC Gastroenterol, 2014. **14**: p. 117.

275. Taylor, M.C., et al., *Factors associated with the high cost of liver transplantation in adults.* Canadian Journal of Surgery, 2002. **45**(6): p. 425-434.

276. van Asten, M., et al., *The increasing burden of NAFLD fibrosis in the general population: Time to bridge the gap between hepatologists and primary care.* Hepatology, 2017. **65**(3): p. 1078-1078.

277. Caballeria, L., et al., *High Prevalence of Liver Fibrosis Among European Adults With Unknown Liver Disease: A Population-Based Study.* Clin Gastroenterol Hepatol, 2018.

278. Koehler, E.M., et al., *Presence of diabetes mellitus and steatosis is associated with liver stiffness in a general population: The Rotterdam study.* Hepatology, 2016. **63**(1): p. 138-47.

279. Kwok, R., et al., *Screening diabetic patients for non-alcoholic fatty liver disease with controlled attenuation parameter and liver stiffness measurements: a prospective cohort study.* Gut, 2016. **65**(8): p. 1359-1368.

280. Roulot, D., et al., *Concomitant screening for liver fibrosis and steatosis in French type 2 diabetic patients using Fibroscan.* Liver Int, 2017.

281. Nobili, V., et al., *Performance of ELF serum markers in predicting fibrosis stage in pediatric non-alcoholic fatty liver disease.* Gastroenterology, 2009. **136**(1): p. 160-7.

282. M, H. and S. K, *Making Every Contact Count (MECC): Consensus Statement.* Public Health England (PHE), April 2016.

283. Gate, L., et al., *Promoting lifestyle behaviour change and well-being in hospital patients: a pilot study of an evidence-based psychological intervention.* J Public Health (Oxf), 2016. **38**(3): p. e292-e300.

284. Barron, E., et al., *Progress of the Healthier You: NHS Diabetes Prevention Programme: referrals, uptake and participant characteristics.* Diabet Med, 2017.

285. Excellence, N.I.f.H.a.C., *Obesity: identification, assessment and management. Clinical guideline.* 2014.

286. Caiazzo, R., et al., *Roux-en-Y gastric bypass versus adjustable gastric banding to reduce nonalcoholic fatty liver disease: a 5-year controlled longitudinal study.* Ann Surg, 2014. **260**(5): p. 893-8; discussion 898-9.

287. Lassailly, G., et al., *Bariatric Surgery Reduces Features of Nonalcoholic Steatohepatitis in Morbidly Obese Patients.* Gastroenterology, 2015. **149**(2): p. 379-88; quiz e15-6.

288. Naveau, S., et al., *The diagnostic accuracy of transient elastography for the diagnosis of liver fibrosis in bariatric surgery candidates with suspected NAFLD.* Obes Surg, 2014. **24**(10): p. 1693-701.

289. Rowe, I.A., *Too much medicine: overdiagnosis and overtreatment of non-alcoholic fatty liver disease.* Lancet Gastroenterol Hepatol, 2018. **3**(1): p. 66-72.